

# ANNALS OF THE RHEUMATIC DISEASES

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# A "NEW ERA" IN RHEUMATISM TREATMENT

FOREWORD BY LORD HORDER

Publication of the *Annals of the Rheumatic Diseases* as a quarterly journal by the British Medical Association marks a new stage in the British effort, dating back several years, to make a worthy contribution to scientific literature dealing with the problems of rheumatic disease. This new stage is welcomed by the Empire Rheumatism Council as assisting its own aim to promote, among the general body of medical practitioners, the degree of interest which the importance of these problems demands. Rheumatism, because of its wide prevalence and its resulting pain and disablement, is perhaps the most serious enemy of social well-being. To check, and ultimately to end, its ravages is a challenge to all branches of our profession—the family doctor, the specialist, and the research worker.

The *Annals* have had a decade of not undistinguished history. In the first place they took the form of an annual published by the British Committee on Chronic Rheumatic Disease appointed by the Royal College of Physicians, and edited by C. W. Buckley, M.D., F.R.C.P. Of this annual four numbers were issued, embodying a considerable number of authoritative articles by distinguished contributors. In 1938 that committee passed on its work, including the publication of the Reports, to the Scientific Advisory Committee of the newly-formed Empire Rheumatism Council. An Editorial Committee was constituted of C. W. Buckley, M.D., F.R.C.P., W. S. C. Copeman, M.D., F.R.C.P., A. G. Timbrell Fisher, M.C., F.R.C.S., and Mervyn Gordon, C.M.G., F.R.S., D.M., and the first number of the new series was published in January, 1939.

First as a quarterly and then, when war conditions enforced paper economy, as a half-yearly, the review maintained a high scientific standard. What was among the last important papers from the pen of Ludwig Aschoff appeared in its issue of July, 1939. In 1942 Dr. Philip S. Hench and Dr. Loring T. Swaim of the United States became Associate Editors, and the *Annals* thus became an Anglo-American organ of medical research in rheumatism. This year the new series opens and I have confidence that it will carry on the good record of the past with an increasing scope for its educational work.

\* \* \* \*

It is the opportunity for that increasing scope which I want to impress. A new era is opening in the public attitude to the rheumatic diseases. At last there is acknowledged the seriousness of the attack which they make on home happiness and industrial efficiency. The old attitude was a very

strange phenomenon. The National Health Insurance Act—purporting to provide for the medical needs of the under-privileged sections of the community—implicitly, if not explicitly, recognized that the efficient treatment of rheumatism called for some special measures other than those available to the general practitioner or the general hospital. Provision was made for the approval by the Ministry of Health of clinics equipped to provide special treatment for rheumatic sufferers; but the number of such approved clinics has up to the present date represented only a "token payment" if we take into consideration the number of sufferers. An Approved Society under the Act could pay for rheumatism treatment if, and only if, its finances were so prosperous that it had a surplus after meeting its other expenses; then rheumatism treatment could be provided as an "Additional Benefit." The effect of these two obstacles was nugatory so far as the great majority of sufferers were concerned. Only those who were insured with a prosperous Society, and were within reach of an approved clinic, could benefit.

Now, the Ministry of Health is pledged to provide for all "treatment appropriate to their needs." We have definite assurances (in Parliament and out of it) that this includes rheumatic sufferers. The White Paper on 'A National Health Service,' neglecting to make specific mention of rheumatism in its short catalogue of diseases, raised doubt in some minds. Was it intended that the word "all" should be construed by the political mind to mean "all, except that very large section of the community which has the misfortune to suffer from rheumatism?" These doubts were subsequently removed by definite assurances. It may be perhaps surmised that the omission of any reference to rheumatism in the White Paper is to be explained by a reluctance to call attention to that very strange phenomenon to which I have just referred, and the consequent necessity to put on the garb of the penitent in confessing to the absurdity of the "Additional Benefit" system. What is very reassuring is the fact that the Minister has quite recently set up a subcommittee of his Medical Advisory Committee to consider the whole position relative to the rheumatism problem and to report to him for his guidance.

But the past may be left as the past and the new era gratefully welcomed, with note of two developments which will be consequential on the decision to provide "treatment appropriate to their needs" to all rheumatic sufferers, instead of, as at present, to only about 10 per cent. of their number.

The first development will obviously be to make a great additional demand on the medical profession and its auxiliaries. This fact, with its implications, must be squarely faced; otherwise the hope held out to neglected sufferers may prove illusory.

One of those implications the Empire Rheumatism Council recognizes in the plans it is preparing—to promote as soon as practicable a series of post-graduate courses in rheumatism treatment for medical practitioners. The aim of these will be to provide sufficient special knowledge, especially as to the resources of physical medicine, to fit doctors to take charge of local treatment centres with a “reserve” of a few specialized centres to which particularly difficult cases could be referred. These specialized centres would also have the duty of research into the causative factors of the various morbid conditions now classified as rheumatic as well as clinical research into proposed new methods of treatment.

It is my conviction (and that of my colleagues of the Empire Rheumatism Council) that it would be a serious mistake to attempt to divorce rheumatism treatment from the general body of medical practice. I may be permitted on this point to quote the argument supporting it from “Rheumatism—A Plan for National Action,” in which it is stressed that the method to be adopted should be consistent with our existing medical system.

“That system assumes that the general practitioner has a sound knowledge of medicine and surgery because, before he can become a qualified doctor, he must submit to a lengthy course of training and prove by examination that he has gained the knowledge which is the fruit of that training. This assumption is justified, with few exceptions; probably there is a lower average of incompetents in the medical than in other professions. In any case we should come to an *impasse* if we have not faith in the general practitioner as normally skilful in the diagnosis and treatment of human illness. The best resource, indeed, of any sufferer, in the first instance, is the ‘family doctor’; he (or she) can deal with the average case and can decide when specialist or institu-

tional advice is necessary. We must accept this or deny the efficacy of our whole medical system.

“Let us decide then, that in the treatment of rheumatic disease it is sound to follow the method of relying on the main body of the medical profession, with reserve forces of rheumatological specialists and institutions at hand to reinforce them as necessary.

“But obviously there is need, and a need which will increase as we get to closer grips with the rheumatic problem, for increase in the number of those specialists; and an equally urgent need that the general body of practitioners should be encouraged to devote some particular attention to the problems of rheumatic disease. In its treatment the best hope of success rests in the capacity to detect, or at least to suspect (and, following the suspicion, to seek further advice) the first symptoms of rheumatic disease. Like all other ideals, it is, humanly speaking, impossible of complete attainment; but it must be pursued steadily.”

To that argument there might be added, with reference to the past rather than the future, that it has not been the fact that the “family doctor,” in general, was ignorant of the particular means needed for the treatment of some forms of rheumatic disease. It was, rather, the fact that it was futile to prescribe treatment which it was impossible for the patient, in the majority of cases, to obtain. The provision of treatment Centres was thus a first necessity.

\* \* \* \*

The second development is full of hope for the future. With the provision of treatment “appropriate to their needs” for rheumatic sufferers there will become possible that early attention to a condition causing or threatening the development of rheumatism, which is the primary need. There will also be provided the facilities (not at present existing to anything like the necessary extent) for intensive and effectively controlled clinical research to evaluate accurately the efficiency of present methods and proposed new methods of treatment.

In this new era of promise it may well be that the *Annals*, in some near future number, can chronicle a steady diminution of the ravages of rheumatic disease.

HORDER.

## EDITORIAL FOOTNOTE

The decision of the Empire Rheumatism Council to seek publication of the *Annals* by the British Medical Association has been responsible for some delay in the issue of the first number of volume iv, and for the new format. It is hoped that this development will increase the circulation of the *Annals* as the leading publication on rheumatic diseases in the English-speaking countries.

The exigencies of the paper supply will influence the regularity of publication, but it is hoped to maintain quarterly issues. The next number will include a continuation of Lieut.-Colonel W. S. C. Copeman's observations on the experimental transmission of rheumatism, an important paper by Mr. Norman Capener, and a paper from Australia on fibrositis.

In the U.S.A. the establishment of a rheumatism

centre at the Army and Navy General Hospital, Hot Springs, Arkansas, is an important step. It is hoped to publish a full account of this. In a letter to the Chairman of the Empire Rheumatism Council, Lord Horder, Lieut.-Colonel Hensch mentions that a small-scale research has just been completed on the effect of penicillin on rheumatoid arthritis. High doses were given for fairly long periods of time without result. Several groups of doctors have used penicillin for rheumatic fever, but again without result; one physician made the pungent remark: “The use of penicillin allows one to study the natural course of events in rheumatic fever.”

The Editors will be glad to consider for publication in the *Annals* papers on the rheumatic diseases, and especially reports on research work, either clinical or laboratory.

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# THE NODULES AND LYMPH-GLAND ENLARGEMENT IN RHEUMATOID ARTHRITIS

## ALSO A SYNDROME OF RHEUMATOID ARTHRITIS COMBINED WITH MULTIPLE XANTHOMATOUS CONNECTIVE TISSUE INFILTRATIONS

BY

F. PARKES WEBER

In this paper I shall consider the nodules of rheumatoid arthritis and some of the clinical features of cases in which they occur, including the occasional moderate painless enlargement of superficial lymph glands.

Collins (1937) and others have shown that the characteristic subcutaneous nodules consist of foci of fibrinoid degeneration and necrosis, surrounded by a border of tissue reaction, notably by a palisade-like radiate arrangement of fibroblasts. Obviously such a microscopic appearance cannot be absolutely pathognomonic—showing as it does a primitive type of reaction towards a central degenerative or necrotic core of unknown causation, the whole process perhaps commencing as an acute focal exudative lesion. Indeed, similar appearances have been described in granuloma annulare,\* and Dr. W. Freudenthal has shown me microscopic sections in illustration, though granuloma annulare is clearly a condition of totally different nature. No exact aetiological explanation of the nodules will be possible before the main causative agent of the rheumatoid disease has been discovered.

The identity of rheumatic fever with rheumatoid arthritis cannot be proved by any histological resemblance between such primitive types of reactive lesions as Aschoff bodies and the relatively transitory "rheumatic nodules" in children suffering from rheumatic fever and chorea on the one hand, and on the other the nodules of rheumatoid arthritis. It is now universally acknowledged that various pathogenic agents (living or not-living) may produce the same reactive or degenerative macroscopic or microscopic picture; also that a resulting lesion may largely depend on, and morphologically vary according to, the reactive qualities of the "soil" on which an identical agent works. It must be admitted on the clinical side that there are subacute or chronic cases of rheumatic fever in adults, especially those affecting mainly the small joints of the hands, which—for a time at least—very much recall the clinical features of rheumatoid arthritis and in which the differential diagnosis may be at first difficult. For

the matter of that it is not always so very easy clinically to differentiate osteo-arthritis ("degenerative arthritis") from rheumatoid arthritis. Certainly pathological changes of both categories may occur in the same patient, as would seem *a priori* probable. Indeed, one would think that a patient with chronic rheumatoid arthritis is more likely than others to develop some of the degenerative changes of osteo-arthritis, and vice versa. I do not know, however, of any case in which a patient with osteo-arthritis, unmixed with rheumatoid arthritis, has developed subcutaneous nodules (of the rheumatoid arthritis type) or moderate painless enlargement of superficial lymphatic glands (of the rheumatoid arthritis type—see further on). It is said, indeed, that the very rare *large* type of "bone-cyst" above the acetabulum has been found in osteo-arthritis as well as in rheumatoid arthritis. Thus, Burt (1942) illustrates an example in rheumatoid arthritis, whilst Alexis Thomson (1929) figured similar "cysts" as from a case of osteo-arthritis. Of great importance is the fact that patients with symptoms (for a time at least) more or less clinically like those of rheumatoid arthritis may present nodules and juxta-articular infiltrations which on microscopic examination are found not to conform to the rheumatoid arthritis type. But to this subject I will return further on.

### Some Case Histories

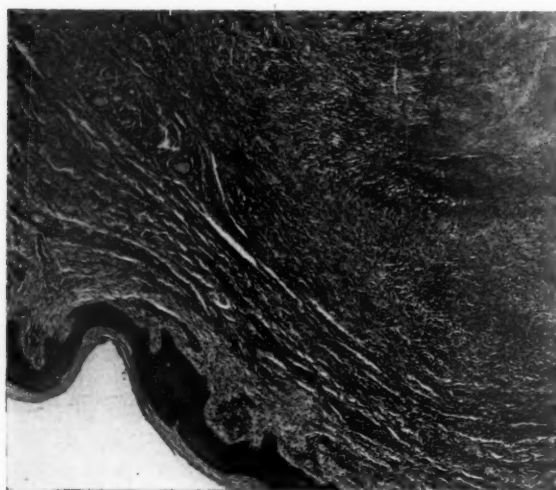
I have mainly selected rather "exaggerated" examples, in which in addition to ordinary changes of chronic rheumatoid arthritis there were subcutaneous nodules—in one case a smaller nodule, more cutaneous than subcutaneous, could be examined by biopsy—enlarged synovial bursae with thickened walls, ganglia of the hands or wrists, juxta-articular thickenings of tendon insertions or tendon-sheaths, and moderate painless enlargement of superficial lymphatic glands.

#### CASE 1

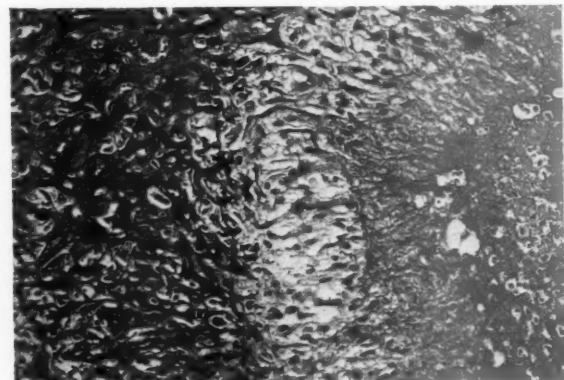
Mrs. A. B. Aged 56 years. Has had rheumatoid arthritis for 25 years. The chief changes are in the hands and wrists. Large wrist ganglia. Lesser changes in the feet, elbows, and knees. Subcutaneous nodules about

\* I understand that microscopically the so-called "lipoid necrobiosis" (not confined to diabetics) is a somewhat analogous necrotic lesion, but containing lipoids.

affected joints. Large lobulated ones at the elbows are connected with the olecranon bursae. Small ones over knuckles of fingers and toes and over both patellae. These latter, which developed rapidly and almost painlessly within the last weeks, feel like tense cysts and are not definitely attached either to the cutis or to the periosteum. There is a large, fluctuating, ganglion-like swelling at the back of the right wrist from which there are hernia-like protrusions. Blood count: Hb. 58 per cent.; erythrocytes 3,900,000 per c.mm.; C.I. = 0.73; leucocytes 10,400 per c.mm. (polymorphonuclears 58 per cent.; lymphocytes 31 per cent.; monocytes 5 per cent.; eosinophils 5 per cent.; basophils 1 per cent.). Blood-Wassermann reaction: negative. Urine: nothing special. Brachial blood pressure: 150/90 mm. Hg. Blood cholesterol: 220 mg. per 100 c.cm. Blood urea: 30.5 mg. per 100 c.cm. Blood uric acid: 4.1 mg. per 100 c.cm. Basal metabolic rate: +10. There is moderate painless enlargement of lymphatic glands in both axillae. No enlargement of liver or spleen. Some pyorrhoea alveolaris. Nothing else of importance by ordinary examination. Recent dietetic treatment for gastric ulcer has been successful.



A



B

FIG. 1. Case 1: Photomicrograph from a section of the left olecranon bursa, which has been transformed into a lobulated massive nodule of the "rheumatoid arthritis type." It shows a necrotic centre with radiate reactive border. A. Under low power. B. Under high power.

**Biopsy.**—My colleague, Mr. H. Rast, kindly excised the whole of the subcutaneous, enlarged, lobulated left olecranon bursal mass, in which there was only a minute synovial cavity left. The bursa was transformed into a mass of small hard nodules, one of which was so superficial as actually to be in the cutis. The mass was elongated, measuring 6.5 cm. (in length), 3.5 cm. (in width), and 2 cm. (in depth), and on incision presented an anaemic, whitish, somewhat gelatinous appearance. Following is Dr. J. G. Greenfield's histological report (see Fig. 1 A and B): "The central core of the tissue consists of a structureless unnucleated—i.e., necrotic—tissue which in Van Gieson sections shows a varying amount of collagen. In some places it forms a loose network, in others thicker strands. The outlines of old obliterated blood vessels can also be recognized. Round this core there is a dense wall of viable collagen (i.e. nucleated connective tissue with thick collagen fibres), with a palisaded zone of radially arranged fibroblasts between the viable and necrotic tissue. In one place

early necrosis is taking place; here and there are many degenerated neutrophil leucocytes as well as a smaller number of coarsely granular eosinophils. Lymphocyte and plasma-cell infiltration is present in the lymphatics of the dermis. No giant-cells seen." The photomicrographs (Fig. 1, A and B) show a necrotic centre with radiate reactive border of the "rheumatoid arthritis type."

#### CASE 2

C. D. Aged 48½ years. An office clerk (Weber, 1943; Case 2). Rheumatoid arthritis of three years' duration. Large cutaneous-subcutaneous nodules about the joints, with juxta-articular infiltrations in the tendon sheaths and fibrous structures about the feet, ankles, hands, wrists, elbows, and knees. Most striking are the red shiny nodules over the metacarpo-phalangeal articulations and about the elbows—up to the size of large cherries (Fig. 2). The knees, ankles, and feet are similarly affected, but the nodules are less red. Very characteristic are the nodules along the ridge of the ulna of both forearms, from elbow to wrist. Moderate painless enlargement of the inguinal, axillary, and supracondylar lymphatic glands. No obvious splenomegaly. None of the nodules are really painful or tender. The tendon sheaths at various parts are infiltrated, notably in the palms and at the heels

(Achilles tendons). The distribution of the nodules and infiltrations is markedly symmetrical. There is some stiffness at the back of the neck, and owing to the condition of the knees the patient cannot bend forward properly. The hands are stiff and show some subluxation of joints. The fingers are said to turn dark blue nearly every morning in cold weather. Ordinary examination of the thorax, abdomen, and urine shows nothing special. Erythrocyte sedimentation rate greatly accelerated. Blood-Wassermann and Kahn reactions negative. The blood cholesterol is rather on the low side. The teeth were all removed at least twelve years ago. About that time the patient was found to have a duodenal ulcer (confirmed by x-ray examination).

**Biopsy.**—microscopic examination of one of the nodules (Fig. 3) shows connective-tissue reaction, with foci of fibrinoid degeneration and necrosis, surrounded by palisade-like, radiate borders of fibroblasts, as described by Collins (1937) in regard to the subcutaneous nodules of rheumatoid arthritis.



FIG. 2. Case 2 : Photograph of nodules on upper limbs, July, 1941.

CASE 3

E. F. Aged 59 years. English. A stonemason, working at present as a post-office packer. Rheumatoid arthritis of at least five years duration. On the whole, however, an active man, of "wiry" type. Hard subcutaneous nodules about the size of an olive over ulnar ridge near either elbow, of about six months' duration, not painful, but slightly tender to pressure. Moderate, painless, symmetrical enlargement (the patient was unaware of this) of lymphatic glands in axillae and groins. No enlargement of spleen or liver. Tense, cyst-like,

pea-sized, painless nodule over the proximal interphalangeal joint of the right fourth finger, which appeared about twelve months ago, suddenly (as patients say such small nodules of rheumatoid arthritis do). This was a cutaneous rather than a subcutaneous nodule. He also has moderate flabby enlargement of the right olecranon bursa, which hurts slightly if he leans on it. Some stiffness and ulnar deviation of the fingers of the right hand. Slight stiffness in cervical spine. He had other symptoms formerly that disappeared under treatment. No history of gonorrhoea or syphilis. Nothing special by ordinary examination of thorax, abdomen, nervous system, and urine. Slight anaemia. Blood sedimentation: slightly accelerated. Blood-Wassermann reaction: negative. Blood cholesterol: 345 mg. per 100 c.cm. Blood calcium: 9 mg. per 100 c.cm. Blood urea: 43 mg. per 100 c.cm. Blood uric acid: 3.2 mg. per 100 c.cm.

*Biopsy.*—My colleague, Mr. H. Rast, excised the above-mentioned nodule from the knuckle of the right ring-finger, and it was carefully examined by Dr. W. Freudenthal. It showed multiple foci of so-called "fibrinoid degeneration" and necrosis (as described by Collins, 1937), some of them surrounded by a palisaded border of fibroblastic reaction; elastic fibres practically absent from the degenerative areas; no giant-cells seen.

Remarks

Even if the histological features of the nodules of rheumatoid arthritis were absolutely pathognomonic one would still be far from the discovery of the essential pathogenic agent of the disease. But, as I have already pointed out, the type of lesion in question cannot be regarded as really pathognomonic. Allison and Ghormley (1931) (compare also Ghormley, 1938) made a great point of what they call "focal collections" of lymphocytes in the synovial membrane of joints being almost pathognomonic of "proliferative arthritis of uncertain origin"—that is to say, of rheumatoid arthritis. They write (p. 139): "Diagnosis made positive on discovery in the tissues of focal collections of lymphocytes." But if one looks at their illustra-



FIG. 3. Case 2 : Photomicrograph of a section from a subcutaneous nodule showing typical necrotic focus with radiate fibroblastic border.

tions (for instance, p. 147, Fig. 4; p. 169, Fig. 3; and Plate VIII) one recognizes the presence in these "focal collections" of so-called "germ-centres" of Flemming. Now, surely such lymphadenoid foci with typical "germ centres" can hardly be considered as pathognomonic of any special disease. Apart from their conspicuous presence in normal lymphadenoid tissue (lymph glands, tonsils, the walls of the vermiform appendix and intestines, the Malpighian corpuscles of the spleen), they form a special feature in so-called lymphadenoid goitres, and are also not rare in thyroids from patients with Graves's disease. I have seen them in abnormal salivary glands. They constitute a conspicuous feature of cutaneous lymphocytomata (Epstein, 1935), and may be found in various other pathological conditions.

#### The Painless Lymphadenopathy

Neither is there anything absolutely pathognomonic in the painless lymphadenopathy of the superficial lymph glands, which is present in many cases of rheumatoid arthritis, though seldom noticed by the patients themselves and often not looked for by the examining doctor. I myself have had a biopsy in only one of my cases, but I believe that the finding is typical for other cases also—namely, a non-specific "follicular lymphadenopathy" of toxic or infective origin, with marked enlargement of the "germ-centres" of Flemming. This must of course not be confused with the early stages of "follicular reticulosis" or "follicular lymphoblastoma" of non-inflammatory (neoplastic) origin.

#### CASE 4

Mrs. G. H. Aged 65 years. Of thin, wiry build, was under treatment in 1941 and 1942 for rheumatoid arthritis. She had suffered from lobar pneumonia of the right upper lobe in the spring of 1939. In Sept., 1940, she began to suffer from rheumatoid arthritis, afterwards located notably in the hands, with some fusiform swelling of the finger-joints. There was also considerable stiffness of the cervical spine. Some moderate discrete painless enlargement of superficial lymph glands in neck, axillae, and groins, of which patient herself was unaware. No enlargement of spleen or liver. Brachial blood-pressure: 190/90 mm. Hg. Some hypertrophy of the left ventricle of the heart, apparently from high blood-pressure. Trace of albumin in the urine. Blood count (July 1, 1941): Hb. 65 per cent.; erythrocytes 3,580,000 per c.mm.; C.I.=0.91; leucocytes 6,150 per c.mm. (polymorphonuclears 71 per cent.; lymphocytes 21 per cent.; monocytes 6 per cent.; eosinophils 1 per cent.; basophils 1 per cent.).

*Biopsy.*—On Sept. 12, 1941, Mr. Rast excised one of the enlarged lymph glands from the right axilla. Dr. J. G. Greenfield's microscopical report (Fig. 4) is: "The sections show general proliferative activity, with many mitoses, in the lymphoid centres; and occasional collections of polymorphonuclear cells in relation to the sinusoidal systems. There is also a slight fibrosis of the gland. These are all evidences of toxic or bacterial stimulation of no specific type."

When the patient left the hospital on Nov. 13, 1942, she could walk almost normally, and no enlargement of

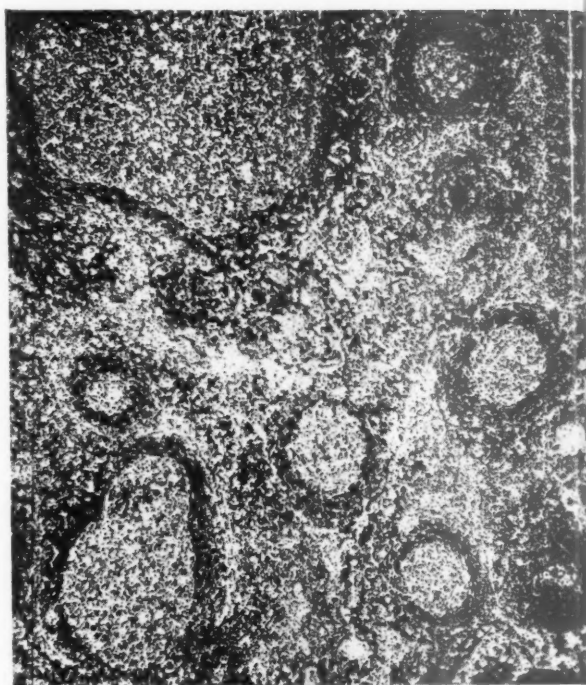


FIG. 4. Case 4: Photomicrograph of a section from an enlarged lymph gland showing toxic or infective "follicular lymphadenopathy" with large germ-centres.

any superficial lymph glands could be felt, excepting the inguinal glands, and that very slight and on the right side only.

#### A Syndrome of Rheumatoid Arthritis Combined with Multiple Xanthomatous Connective-Tissue Infiltrations

There are other subcutaneous nodules and infiltrations which might in rare cases be confused with those of rheumatoid arthritis (Weber, 1943), but I shall here confine myself to a condition which seems to be genuine rheumatoid arthritis associated with multiple xanthomatous nodules and infiltrations, especially about the joints and in the subcutaneous (occasionally cutaneous) tissue.

The special case that I shall fully record here has been under observation for several years. I described it originally with Dr. W. Freudenthal in 1937 and later in 1943 (Weber and Freudenthal, 1937; Weber, 1943), but can find no literature on the subject excepting perhaps Layani's case of "Xanthomatous chronic deforming rheumatism" (Layani, 1939; Layani and others, 1939). Layani's case was that of a woman, aged 46 years, who had a deforming rheumatoid disease of fifteen years' duration. In addition to the xanthomatous condition she had prolonged jaundice with hepatomegaly, and there were other remarkable features in the account.

However, owing to the kindness of Dr. George Graham and Dr. E. T. D. Fletcher, I have been able to examine two other men in England apparently suffering from a somewhat similar syndrome. I

hope that an account of these two cases will appear in due course. As I have been given kind permission to refer to these cases with my own one, I will here emphasize the point that hypercholesterolaemia seems not to be an essential, and is certainly not a constant symptom. Another point is that the infiltrations tend to be greatly in excess of those generally recognized as an occasional feature in typical rheumatoid arthritis. In all three cases there was strong evidence that the application of heat made the xanthomatous infiltration worse. This was pointed out to me by Dr. Graham from various observations in his own case, and it may be of some therapeutic significance. Dr. Fletcher's patient believes that radiant-heat therapy (which was given previously to seeing Dr. Fletcher) had made his trouble rather worse than better. Both my patient and Dr. Graham's patient developed a florid increase of the subcutaneous infiltrations—which tended to become actually confluent in parts over their shoulders and backs (the specially hot parts) after they had been lying for days on their backs in bed. Another remarkable feature in both Dr. Graham's patient and mine was the occurrence (in addition to the large and medium-sized nodules) of minute (miliary) superficial nodules ("droplets"), evidently arising in the outer part of the cutis; these appeared for a time in great numbers on the nose, forehead, and other parts of the face, and then disappeared without leaving a trace. In my case the ultimate atrophy or involution of the large nodular infiltrations tended to be more complete than that which occurs in acknowledged cases of rheumatoid arthritis. Finally, I cannot help thinking that the xanthomatous infiltrations in these little-known cases may have a relation to the rheumatoid arthritis analogous to that which gouty tophaceous deposits sometimes appear to have to osteo-arthritis with

exaggerated Heberden's nodes. It may be remembered, by the way, that Chauffard and others (1921 and 1923) found that tophaceous deposits contained a considerable admixture of cholesterol. In Dr. Graham's case a large sarcoma-like growth ultimately developed. This reminds me of the possible though doubtless exceedingly rare relation of sarcoma to benignant so-called "xantho-myeloma of tendon sheaths," and perhaps it might also be compared to the very rare supervention of frank spindle-celled sarcoma in "multiple idiopathic haemorrhagic sarcoma" of Kaposi (which is generally considered not to be a true sarcoma). I well remember this occurring in an old case of Sequeira's (Sequeira and Brain, 1926).

#### CASE 5

This case was demonstrated by Parkes Weber and Freudenthal at the Royal Society of Medicine in Dec., 1936 (Weber and Freudenthal, 1937), under the heading "Nodular non-diabetic cutaneous xanthomatosis with hypercholesterolaemia," but the presence of cholesterol in the lesions was not absolutely proved, and the hypercholesterolaemia was certainly not constant. Following is the account of the case up to the time of the demonstration in 1936.

K. L. A man aged 35, general labourer, began six months ago to suffer from pains and stiffness in various joints, which obliged him to give up work. Since then he has had varying swelling of the knee-joints and of the tendon sheaths at the back of the wrists, now hardly noticeable. During the last six months cutaneous nodules (freely movable over the deeper parts) have been appearing on the hands, mostly on the back of the fingers and thumbs, especially near the joints; they are hard and reddish, averaging a small pea in size (Fig. 5). During the same period similar nodules appeared over the ulnar ridges, up to the size of a cherry over the right olecranon (Fig. 6); two pieces were excised for biopsy purposes from the left elbow, and one pea-sized nodule from over



FIG. 5 Case 5 : Photograph of the right hand, Nov. 14, 1936.



FIG. 6. Case 5 : Photograph of the right elbow, Nov. 14, 1936.

the base of the left index finger. Numerous smaller nodules are to be seen over the external ears, and still smaller ones (really miliary or minute) on the face, especially over the borders of the lips and nostrils. Some of the minute facial nodules have a yellowish-red colour. None of the nodules have been itching or painful or tender to pressure, except the large ones at the elbow. Recently, in December, fresh nodules, mostly red, have appeared about the elbows, over the back of both great trochanters, over the buttocks, and over the coccyx in the intergluteal fold. There is now also a conglomerate or confluent nodular plaque over the back of both acromial regions—more pronounced on the right side, on which the patient usually lies. It is highly probable, as I stated above, that this florid exacerbation of the subcutaneous infiltrations was induced by local heat due to the patient lying for days in bed. His body-weight is 53.2 kilogrammes, against (apparently) 60 kilogrammes early in November.

There is nothing especial in the past history, excepting dysentery in 1920 in India. The patient was kindly handed over by Dr. M. B. Ray, and he was in hospital under my observation from Nov. 14, 1936 to April 1937.

In the hospital there was occasional slight fever in November. By ordinary examination of the thorax and abdomen and by x-ray examination of the thorax and bones of the hands and feet, nothing abnormal is found; nor is there anything special to be noted in regard to the nervous system and eyes (fundus normal) and internal parts of the ears, nose, and mouth (including pharynx). There is no thickening of the ulnar nerves at the elbows. The urine shows nothing abnormal (unless very slight excess of urobilinogen), and no alimentary glycosuria follows the ingestion of 50 g. glucose. Fasting blood sugar: 0.07 per 100 c.cm. Blood-sugar curve normal. Blood-serum cholesterol on the first occasion was 230 mg. per 100 c.cm., and on the second 350 mg. per 100 c.cm. Fractional examination of the gastric contents shows complete absence of free hydrochloric acid even after a subcutaneous injection of histamine; pepsin

present. The blood serum, which is clear but somewhat over-coloured, gives a negative direct, but positive indirect, Van den Bergh reaction. Wassermann and Meinicke reactions: negative in the blood. Pirquet cuti-reaction: negative. Blood sedimentation: not decidedly accelerated. Blood urea: 36.5 mg. per 100 c.cm. Blood uric acid: 3.7 mg. per 100 c.cm. Non-protein nitrogen in the blood: 30.5 mg. per 100 c.cm. Blood-serum calcium: 8.5 mg. per 100 c.cm. Blood count (Nov. 24): Hb. 84 per cent; erythrocytes 4,500,000; leucocytes 3,500 per c.mm. (eosinophils 7 per cent.; polymorphonuclear neutrophils 45 per cent.; lymphocytes 45 per cent.; monocytes 3 per cent.).

*Biopsy.*—Histological report by Dr. W. Freudenthal (Figs. 7, 8): The main change seen in the sections is the presence of large masses of cells, which form round, or oval more or less, defined areas, and are scattered irregularly between the bundles of the collagen tissue in all parts of the cutis. The cells are so numerous that their mass exceeds that of the collagen tissue, the bundles of which are pressed aside rather than destroyed. These cells are conspicuous by their size, which is up to four times that of an epithelial cell. Most of them are multinucleated and have three to five or more bright nuclei (with definite nucleoli), frequently aggregated. They have a well-stained, well-defined, abundant, round, oval or polygonal cytoplasm. Most of the cells are clearly defined; sometimes neighbouring cells are connected by cytoplasmic threads giving them a certain resemblance to prickly cells. The cytoplasm is homogeneous; even by oil-immersion magnification it does not show a foamy structure.

When the sections are stained for fat with Sudan III, these cells in some areas show no fat or lipoid at all; in other areas the cytoplasm is stained a faint red, which is in some places more distinct. No double refraction. Even in the areas in which the cells are stained more distinctly the colour is paler than the bright red of the fat cells of the subcutaneous tissue; the colour of the supposed xanthoma cells has the slightest tinge of brown.



FIG. 7. Case 5 : Photomicrograph of a section from an excised nodule. The epidermis is seen in the upper part of the figure, and the large size of the "pre-xanthoma cells" is obvious by comparison with the size of the epidermis cells.

In fact, it is a question whether the cells ought to be called xanthoma cells at all, for by the term "xanthoma cell" one usually understands a cell the cytoplasm of which is loaded with lipoid droplets ("foam cells"). In our sections the cells show either no lipoid (visible by our imperfect histo-chemical method) or lipoid in a

diffuse form. Merely to call these cells giant-cells would scarcely help us. One could perhaps call them "pre-xanthoma cells" to mark their connexion with typical xanthoma cells. It must be admitted that we have no proof that these cells actually become xanthoma cells. A possible explanation is, then, that these cells represent an intermediate stage in the development towards typical foam cells (cf. Arzt, 1919). Yet it is possible that they are not an intermediate stage, but are at the height of their development, and that their peculiar appearance is due to some special lipoid they contain. Microscopically, it must be admitted, they show a marked resemblance to "Gaucher cells."

*Progress of the Case after Dec., 1936.*—Under a fat-poor diet the blood-serum cholesterol fell to 110 mg. per 100 c.cm. (Feb. 19, 1937), and the nodules decreased, notably the patches over the back of the acromial regions. The patient finally left the hospital in April, 1937. When he was seen again in April, 1941, at the age of 40½ years, there were only remnants of the nodules on the hands and about the elbows. The process of involution had left a little shrivelling of the skin about the left elbow. Rheumatoid troubles were in the foreground, but even in regard to these he thought he was improving. He could get about, but owing to stiffness in the hips he could not stoop sufficiently to pick up anything on the floor. His fingers were rather stiff and slightly deformed. There was some limitation of movement in the left shoulder and a little crackling on movement could be felt over the joint and left scapula. Both knee-joints manifested considerable crackling on movement. The appetite was good. The patient said he was treated at the Middlesex Hospital about 1938-39, where he had all his teeth removed, a fat-poor diet, orange juice with glucose, massage, and injections of some kind.

On Nov. 6, 1943, I was able again to examine the patient, K. L., who said that he was able to walk about well and do night watching (without any medical treatment). In short he had functionally almost recovered, although he could not yet flex his right hip normally. He still had "knotty" rheumatoid hands, with nodules at the knuckles and over the elbows. There was also a good deal of crackling when he flexed and extended his knee-joints.

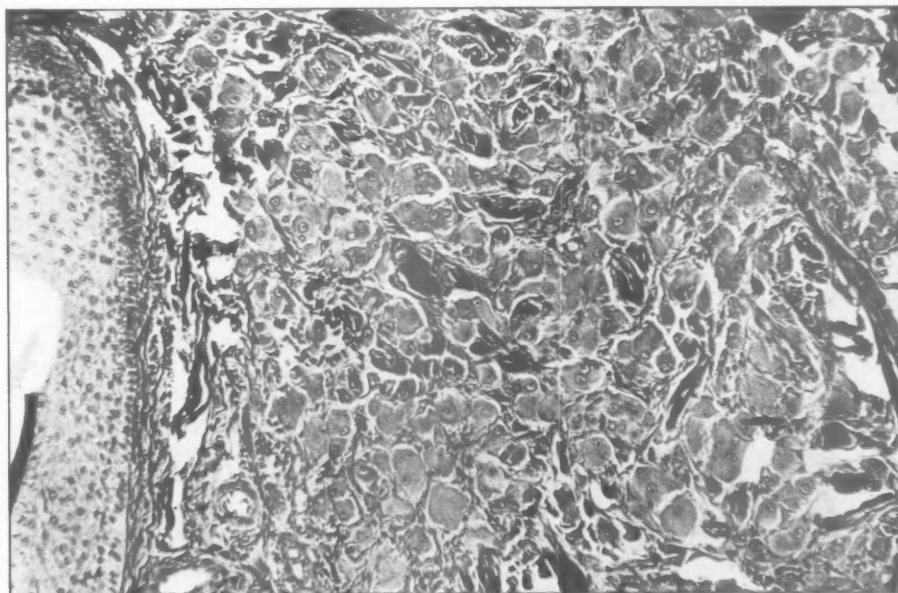


FIG. 8. Case 5 : Photomicrograph of a section from an excised nodule. Hair follicle on the left.

## CASE 6

In June, 1941, a married sister of the patient was seen, Mrs. M. N., aged 43, who was said to be suffering from a chronic rheumatoid disease. She is a well-built woman of about 10 st. 4 lb. in weight. There is chronic thickening of both wrists with limitation of movement. Both elbow-joints cannot be properly extended. The right knee is somewhat flexed and there is crackling on movement. The left knee seems normal. There is thickening around the proximal interphalangeal joint of the left little finger and apparently some infiltration of its flexor-tendon sheath. No other joints are affected, and there are, and have been, no cutaneous or subcutaneous nodules. She has had twelve children, of whom ten are living and well. Her rheumatoid troubles commenced in both hands eighteen months after the birth of her third child, that is to say, about sixteen and a half years ago. She has never had pain in connexion with them she says, except a little aching in rainy weather, and she has never really been laid up. It is possible that her condition is similar to that of her brother, but a very incomplete form of the disease.

## Summary

In this paper the nodules, infiltrations, and painless adenopathy of rheumatoid arthritis, and their pathological significance, are considered.

Attention is also drawn to the existence of a little-known syndrome in which clinical features of rheumatoid arthritis are associated with nodules and infiltrations, apparently of xanthomatous nature, though hypercholesterolaemia seems to be of not necessary (at least, not constant) occurrence. I have described only one case fully (which was first

observed many years ago), but I know of the existence of other cases probably of the same category, two of which will, I hope, be fully described in due course. The interest of this syndrome does not lie in its extreme rarity, but rather in the light which, when more completely studied, it is likely to throw on the pathology and nature of various other groups of cases.

My thanks are due to Dr. George Graham, Dr. M. B. Ray, and Dr. Ernest T. D. Fletcher for enabling me to see and helping me to examine some of the patients, to Mr. H. Rast for carrying out the biopsy excisions, to Dr. W. Freudenthal and Dr. J. G. Greenfield for their microscopic reports and to Dr. Greenfield for photomicrographs, and to the Editors of the *British Journal of Dermatology* and the *Proceedings of the Royal Society of Medicine* for allowing me to use previous papers of mine and blocks for illustration.

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# OBSERVATIONS ON THE NATURAL HISTORY OF ACUTE RHEUMATIC FEVER

BY

W. S. C. COPEMAN

It was remarked in the *Lancet* recently that clinical medicine is the study of man in his environment. It would seem therefore that the more simple the environment can be rendered the less complicated should become the study of his disease.

An unusual opportunity to study the natural history of certain rheumatic diseases in a body of young healthy males was offered by working in a hospital which supplied the medical needs of several large bodies of troops who were stationed, as was the hospital, in a remote desert. Thus they were isolated from all contacts (other than those within their units) for a period of nearly a year, and they were totally divorced from those complicating factors which are associated with civilized environment. As a result it is believed that a clearer understanding of the genesis and development of rheumatic fever and of its relation with fibrositis was obtained. Subsequent experience in Malta soon after the siege (during which a large proportion of the population had been living on a minimal diet in underground caves), allowed an investigation which further conditioned these views. Later, certain invasion troops were seen after a journey involving hardship and exposure unusual even for such "tough" troops as this "spearhead" comprised. This also provided material for study, and some of the results are incorporated in this paper.

## Aetiology of Rheumatic Fever

Rheumatic fever, it is generally agreed, shows unmistakable signs of being due to an infection. It is not primarily caused by the factors of exposure, fatigue, etc., with which it is nevertheless often associated at onset. In this series of cases it was established that the possibility of the infection having been transmitted by extraneous contacts was remote owing to their isolated situation for ten months, and the fact that their last experience of a city was merely one night in transit four months before. They had left England two years previously and had been since in Burma continuously. If therefore the cause of the cases under consideration was infection transmitted by human agency it would seem probable that it had laid dormant for at least fourteen months, and possibly for much longer, as the disease is not common in Burma. If a period of latency be possible for months, the possibility that this period might last for years must also be considered. With

this in view two categories of cases may be briefly reviewed.

### (1) Cases (10) with history of previous attacks.—

It seems reasonable to suppose that these attacks were recurrences of previous ones in England, in view of the facts that the disease is known to relapse, and the unlikelihood of any fresh infection having been met with in the circumstances. If so the infection must have lain dormant during the years intervening since the last attack (a minimum of 2 years, and in some cases 10–15 years), until conditions again became favourable for its recrudescence. Enquiry in this group revealed that in two cases the mother had suffered from acute rheumatic fever.

(2) *First attacks in desert* (32 cases).—It is reasonably certain that these cases had had no contact with any case of active rheumatic fever for a very considerable period, as apart from crossing India 14 months previously they had no urban contacts since leaving England two years before. It seems, therefore, to be a possibility that some at any rate may have acquired their infection before leaving England, but that the circumstances had not hitherto favoured the development of the disease clinically. These cases did not (except in one instance) arise in units in which the relapse cases, referred to above, developed, nor could contact with them be traced. The first case of rheumatic fever admitted to hospital was a first attack, and was the only case recorded in his unit during our stay. The possibility that certain of these infections might even date back to childhood was considered, and it may be significant to record that in this group nine cases gave a convincing history of acute rheumatic fever in one or more parents—generally the mother. It was noted that all the cases suffering with first attacks reported an exceptional previous freedom from any illness, suggesting a high degree of general resistance. The actual attack of rheumatic fever was, however, in all the desert cases preceded by severe or protracted illness of various other types, and in many cases, in addition, by exceptional exposure and strain which would be likely to have lowered such resistance. These observations seem to favour the possibility that the causative agent of rheumatic fever may, like that of tuberculosis, lie dormant in the healthy body the resistance of which is high, and produce signs of disease only when

circumstances conduce to a marked lowering of this.

The cases studied were in widely dispersed units and the question of droplet infection within these units was investigated and dismissed, with the exception of the four cases discussed later under that heading.

#### INFECTION IN PARENTS AND CHILDREN

The relation between infection in the parents and in their children has been referred to above. It appeared in this series of observations that the proportion of parents who had suffered with the disease was higher in the group of patients who developed first attacks in the desert than in the group who were suffering a relapse of the disease contracted originally in urban surroundings.

At my request C. T. Potter investigated this matter in a series of 405 rheumatic children attending his O.P.D. at the Queen Elizabeth Hospital for Children, and reported as follows: Of 290 children (under 7 years old) with growing pains, 10.7 per cent. of their parents had had rheumatic fever. Of 115 children (under 7 years old) with acute rheumatic fever, 7.6 per cent. of their parents had had rheumatic fever. On this he comments that if the disease is the result of transmissible infection, the proportion of children who suffer with rheumatic fever, and whose parents also give evidence of infection, is unexpectedly low. The observations recorded above may explain this, however, since the organism may in fact be directly transmissible from parent to child; but if the latter's resistance is at the time good it may remain dormant until some infection of another type, such as streptococcal tonsillitis, lowers resistance sufficiently, later in life. It is suggested that the series of first attacks in the desert discussed above may be examples of this mechanism. In cases where the resistance is never lowered to the necessary extent it would appear possible that the syndrome of rheumatic fever will never develop, although the subject is in fact harbouring the organism. This rationalizes the clinical observation that the disease is familial but not strictly hereditary.

Such further problems as whether there may, therefore, be "carriers" of rheumatism, and whether an attenuated form (e.g. fibrositis) might develop in infected persons with high immunity, must await the discovery of the causative organism.

#### Nature of Infecting Organism

The streptococcus is widely implicated as being the causative organism of rheumatic fever by virtue of the fact that it is so frequently a precursor of the rheumatic attack. It is also fairly generally agreed that it is unlikely to be the sole causative agent, but, beyond this, exact knowledge does not yet go. Birkhaug's theory of a circulating endotoxin formed by localized streptococci (toxic focus) has not been confirmed, and does not seem to fit the facts as observed in this series; nor does the theory of super-

sensitivity as the result of previous streptococcal infections, suggested by Zinsser and Yu.

Gibson and Thomson (1933) found that one fact emerged from their studies—i.e. an association between infection with haemolytic streptococci and rheumatic fever. This, they said, was not a simple matter of cause and effect, and some other factor must be postulated, such as the presence of another infective agent not yet defined, possibly with some allergic process as a contributing factor. Only in some such way, they think, can the close epidemiological relation between haemolytic streptococci and rheumatic fever be reconciled with widespread distribution of streptococcal infection and the comparatively limited incidence of rheumatic fever. This view of the matter would fit in with the present observations if we except the need to invoke an allergic process.

Regarding the *Micrococcus rheumaticus* of Poynton and Paine, as recent observations have shown that certain cases of chronic meningococcal septicaemia not uncommonly masquerade as rheumatic fever in both adults and children and are indistinguishable except by means of blood culture (*Lancet*, 1940) the suggestion was recently made that this organism may in fact have been a form of meningococcus, which the facilities at their disposal at that date did not permit them to recognize (*Lancet*, 1942). This likelihood is reinforced by the account they give (Poynton and Paine, 1913) of a fatal case of true rheumatic meningitis following an attack of acute rheumatic fever. Necropsy revealed a healing lesion of the mitral valve and turbid fluid over the whole base of the brain; in films from this "diplococci" were seen in numbers. Also in a fatal case of "chorea" which they describe numerous diplococci were found in the perivascular spaces of the pia mater.

Observation of the cases of rheumatic fever which occurred in the Middle East showed that, although a preceding illness was almost invariable, this was by no means usually due to the streptococcus. Streptococcal sore throats, and more commonly streptococcal furunculosis, were not uncommonly the forerunners of an acute attack of rheumatic fever, but such unassociated diseases as the dysenteries, sandfly fever, and malaria were even more common. It seemed, therefore, as though the role of this "preceding" disease must merely be to lower the general resistance sufficiently to allow some further and so far unknown organism, which was either latent or recently acquired, to produce symptoms. The alternative would be to suppose that rheumatic fever is merely a non-specific but peculiar type of host response to all these various types of organism, conditioned possibly by sensitization, as has been postulated by Davidson and others. If the former view be adopted the role of the streptococcus may be considered to be a non-specific one, as in the case of the other diseases mentioned, and the fact that in England and America it comes so largely into the picture may be explained on the grounds that it is the commonest intercurrent infection of a self-

limiting nature encountered in temperate climates; and more especially at those times of year when rheumatic fever is most commonly met with. In the same way those diseases mentioned above as being the common precursors of rheumatic fever in the Middle East are the commonest infections met with in these latitudes.

If this is so, then the streptococcus cannot strictly be said to have a specific relation with rheumatic fever, although its common association in temperate climates is explicable. In unscientific terms it might be suggested that the pathological function of the "preceding infection" is merely to awaken the dormant specific organism. In some cases the latter, lying in a milieu of high resistance, merely "turns in its sleep"—the clinical consequence being possibly the syndrome of "acute febrile myalgia" described below—whilst if circumstances are temporarily favourable it may be awakened fully, and bite viciously at its host.

Streptococcal infection in the throats of children, about ten days before, was correlated with relapse of their rheumatic fever by Coburn in the Northern States of U.S.A., where, as in England, this is the commonest type of subacute infection met with. This did not seem to occur so commonly in the Southern States, however, where it is reasonable to suppose that conditions approximate more to those in the Middle East. He suggested that rheumatic fever is due to a reaction of tissues to the products of the haemolytic streptococcus in predisposed individuals. It might be suggested that such "special predisposition" is in reality latent specific infection, and that the streptococcal infection allows it to become active by lowering body resistance. When these American children were removed to Costa Rica it was found that they did not relapse, although streptococci were still found in the throats of certain of them. This suggests that in the absence of the third element (the physical factor) generally found by us to be necessary—i.e. exposure, cold, etc.—the virulence of this streptococcal infection was no longer sufficient to depress the child's resistance to the stage at which the specific rheumatic organism could become pathogenic. It is generally found that this physical factor is an important one in the development of a case of rheumatic fever, and indeed sometimes may even replace the need for the usual preceding infection if it is sufficiently severe (see next section).

Such evidence as is presented by this series of cases seems to point to rheumatic fever being caused by some organism at present unknown. If it is accepted as unlikely that the present series of cases had met with any source of fresh infection in the desert, it must be considered probable that this organism is able to remain latent in the tissues of healthy individuals possibly from childhood until resistance is lowered by various means amongst which streptococcal infection takes a high place, environmental factors coming next.

The analogy of tuberculosis arises in the conjunction of these three factors; or (if the conception

of the specific organism as being of the nature of a virus—as originally suggested by Schlesinger and Amies be preferred), the analogy of the activating role of secondary mixed infections and climatic conditions on the virus of the common cold must be considered as being somewhat comparable.

#### SPREAD BY DROPLET INFECTION

It has been suggested by Glover and others that rheumatic fever may be an infectious disease, and he reported a number of instances in which outbreaks of rheumatic fever had occurred in communities of young adults. This, he thought, probably resulted from droplet infection from the upper respiratory passages.

This matter was investigated in all the cases in this present series, and only in the case of one workshop unit, from which four cases were received, did it appear to be likely. They were all received during the month of January and the first week of February, 1943, and they had been living in close contact with a fellow craftsman who had had a first attack of rheumatic fever when aged 6, and another lasting six weeks when he was 15. He was now 22 and had suffered with a bad cold for the previous month, although he did not complain of any exacerbation of the chronic backache, which was a legacy from his last acute attack. None of the four patients had caught the cold, although they slept in the same hut, in which there were twenty other men. The clinical features of their rheumatic attacks were similar. They started with a short period of malaise, then stiffness leading to pain in one or more joints, which swelled up on second or third day, when they were admitted. They were sweating and their temperatures rose to 102°–103° F., although they did not admit to feeling really ill. The blood sedimentation rate rose during the attack and slowly resumed the normal about four weeks after the onset. The attack appeared to respond readily to salicylate treatment. In none of these cases had any rheumatism occurred previously (*vide*, later, "benign" type rheumatic fever). A watch was kept upon this unit, but no further cases occurred during the next three months. This unit had no connexion with other units in which cases arose. Being Base troops their standard of fitness was not equal to that of the divisional units, from which all the others were drawn. The following record is of the first case admitted.

Sgt. Age, 25 years. Service, 2½ years. No previous rheumatic history in self or family. Tonsillectomy when 8 years old. Seven days previous to admission slight sore throat (Gram+ diplococci) and on next day complained of stiffness, acute pain, and, later, swelling of right wrist. On following day left ankle painful, and

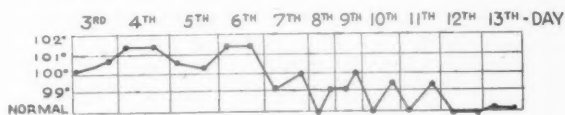


CHART 1.

metacarpal-phalangeal joints of the right hand swollen slightly. After two more days of fleeting pain and B.S.R. 15 mm. the pain and all swelling disappeared and did not return. Two weeks after onset B.S.R. was 7 mm. and he returned to his unit. Four months later, perfectly fit and no recurrence.

### Preceding Factors

Even if we admit the presence in the patient's tissues of an unknown primary infective organism, we must also recognize certain important preceding factors which are almost invariably associated with the onset of the illness. These are: (a) preceding infections of various (non-rheumatic) types, as already mentioned; (b) physical factors, which include unaccustomed or severe exposure, strain, or cold. These two additional factors appeared to be jointly operative in the majority of cases of rheumatic fever which developed in this series, more particularly in the case of the primary attacks. Where the "dosage" of either (a) or (b), however, is extreme, it may prove sufficient to provoke the attack without the necessity for the other factor being operative (*vide*, later, "Cases due to physical factors only").

### NATURE OF PRECEDING INFECTION

Although both the primary and the relapse cases were preceded in nearly all instances by some debilitating illness, both the nature of this and its time relation with the onset of the rheumatic fever were so variable as to render it extremely unlikely that there could be any specific connexion between them. These illnesses were for the most part those which are most common in the Middle East. An analysis of the preceding illnesses in the first twenty-five cases of rheumatic fever yielded the following result: malaria (all types), 8; dysentery (both types), 7; sandfly fever, 6 (in four of these cases two attacks or relapses); streptococcal infections, 4. In most cases the sufferer felt subjectively that he had never entirely recovered from the effect of these at the onset of the rheumatic fever. There was generally a history of exposure in addition occurring during this period. It seemed likely that these illnesses plus the physical exposure acted non-specifically by reducing the general powers of resistance of the body, and so allowing the hypothetical specific organism already present in the tissues to take advantage of this favourable circumstance. Streptococcal infection, although it is the most common preceding infection in England was comparatively rare in this series. Streptococcal sore throats had occurred before the attack in eight of the forty-two cases and streptococcal furunculosis in five. The role of the streptococcus in this connexion has been more fully discussed above under the heading of "the nature of the infecting organism."

It was noted from their histories that all the men infected had had a high degree of immunity to disease in general, rheumatic fever being in most cases their first period of illness since childhood. But for the exceptional circumstances of their present life it

seems reasonable to suppose that many of the cases in this series (who were all category A1 young men), would never have developed rheumatic fever, even though the evidence seems to point to the fact that they were harbouring the specific organism.

A homely analogy may be used to illustrate this relation between the preceding infection and the latent specific infection. In stoves some rapidly burning spirit such as methylated often serves to heat up the heavier but less spontaneously inflammable oil, which will, however, if it reaches the right temperature, initiate even more intense and prolonged combustion. The specificity of methylated spirits for this purpose is perhaps comparable with that of the streptococcus in the rheumatic syndrome, since it is the substance most commonly met with in this connexion in our country, but other volatile spirits (*cf.* organisms) can produce the same effect.

### PHYSICAL FACTORS

These were principally exposure, which includes cold and wet. Whilst the men were in the uplands of Persia they slept mostly in the open. It was extremely cold weather, in many places there was snow, and it rained not infrequently. They slept on the ground. The training during the daytime was intensive and strain was the other principal factor, operating mostly upon those men who had been debilitated by recent illness. In the case of civilian patients investigated later in Malta it is probable that malnutrition also played a part. In the cases which occurred amongst our Sicilian invasion troops exposure and strain were the sole preceding factors, no history of any antecedent illness being obtained. This was the only series of cases in which this seemed to be so.

It was noticeable that where physical factors were operative they were either unusually severe, or else the man was unaccustomed to them. This reinforces the wisdom of the Army policy of progressive "hardening." It appeared that a smaller "dose" of the physical factor was needed to provoke an attack of rheumatism when the antecedent illness had been severe and vice versa—as would perhaps be expected. The site of the initial pains tended to be localized by the nature of the exposure or strain. For example, in several cases where the man had slept on cold ground without a groundsheet the initial lesions were on the side of the body on which the patient had slept, whilst in the cases localized by strain certain joints which had been subjected to this were the first to be affected.

### CASES DUE TO PHYSICAL FACTORS ONLY

The following are condensed case histories of men of commando troops who fell ill after a combined operation. Their attacks were very acute, but ran a "benign" course (*vide*, later, Cases (d) and (e)).

O. A. B. Age, 20 years. Single. Service, 2 years. Father and mother no rheumatic history. Patient had no sickness of any sort except a mild attack of "lumbago" last year as a result of a strain. Last three months

fighting in Tunisia, followed by intensive "invasion tactics" course, which included sleeping in open in wet clothes after swimming ashore. During daytime very long marches with full equipment in great heat. Journey of two days in landing barges in which there was little room to lie down. No shelter from fierce sun, and was rather sea-sick. On last night it rained and he was wet through. On disembarking could not bear weight on left knee as it was very painful. Thought this was due to stiffness and tried to "walk it off," but failed. Went sick next day and was admitted with temperature 103° F. Suffered with typical attack of rheumatic fever of "benign" type (*vide* section on clinical types). Uninterrupted recovery and B.S.R. returned to normal in a month.

C. D. Age, 20½ years. Single. No parental or personal history of rheumatism or other sickness. Was a ghillie before joining paratroops two years ago. One brother and one sister—no sickness. Exceptional exertions involving heavy-weight carrying in Algeria for one week prior to embarkation. During a forced march in great heat had felt giddy and "fainted" but had not gone sick on recovery. For two months had been sleeping in the open on the ground; it was very cold and there was a heavy dew. During the invasion he was shot down into the sea, and spent four hours in the water. The day after he had felt stiff all over, and next morning woke up after a bad night with very tender wrists, knees, and ankles, which all swelled during course of day and became acutely painful. Temperature 100° F. and pulse 100. Admitted.

O. E. Sweating profusely and joints (as above) much swollen and painful. Said he did not feel ill, however, Eyes congested and catarrhal. Constipated. No headache. Temperature was 102.6° F. and pulse 108. There were acutely tender points on the internal aspects of the joints. Next day temperature 100.2° F. and effusion much less, but tender spots, which correspond with points on the tendons of surrounding muscles, as before. B.S.R., 25 mm. This case also ran a "benign" course, and the patient rejoined his unit in five weeks, apparently normal.

It did not seem that these cases differed in any way from those provoked by the more usual mechanism of a preceding illness.

#### GENERALIZED STRAIN

In the only two cases in which cardiac lesions were observed to arise *de novo* the history was of severe strain undergone whilst on a "battle course," in conjunction with a preceding indisposition (sore throat in one, dysentery in the other). There was no exposure experienced.

It is possible that there may be further and less commonly encountered factors which should be mentioned under this heading, although they did not affect the series of cases under consideration. Such factors may include hyperthyroidism, menstruation, etc., and, as already mentioned, sub-nutrition.

#### Nature of Rheumatic Fever: Clinical Observations

The two chief elements of any case of rheumatic fever are (1) the general signs and symptoms, which include pyrexia, malaise, sweating, raised B.S.R., etc., which are common to most generalized infections, and need not be examined further at this

stage; and (2) the local signs and symptoms, which comprise (a) muscle and tendon stiffness and pain, (b) joint stiffness, pain, and swelling, and (c) cardiac lesion.

#### LOCAL SIGNS AND SYMPTOMS: (a) AND (b)

Close observation of these strongly suggests that they are due to a similar "fibrositic" mechanism—probably a localized oedema of the synovium of the affected tendons in the first place, the difference in symptoms and signs depending merely upon the localization and extent of the lesion. A detailed description of the onset of a relapse of rheumatic fever in the first case studied in detail will bring out all the points regarding stiffness, pain, and swelling which emerged as the result of subsequent clinical observation.

L./Cpl. G. H. Age, 32 years. The patient had had two previous attacks of rheumatic fever, the first when aged 12 and the second when aged 15. There were no cardiac lesions, and he was passed into the Army two years before.

A week prior to admission to hospital he had complained of pain in the right ankle for twenty-four hours. The joint then swelled up, this sequence being followed in the left knee on the day of admission. The day after admission (temperature 100° F.) he said that he thought the right knee was going to be affected and also the elbow-joints; these showed no abnormality. On close questioning he described the subjective sensation as a "tightness" round those joints which rendered him rather unwilling to move them, "as they did not feel quite right." By the evening this was interpreted as a definite stiffness; some very localized creakings could be felt over one biceps tendon, and could be heard through a stethoscope. On waking next morning there was "definite pain in all these joints." Close examination showed, however, that this pain was in fact situated in certain tendons around the joints, and that pressure on these areas exacerbated the "joint pain," whilst pressure on other tendons, or areas of the same tendon, as well as along the joint line had no effect. This pain was increased by movement of the joint. The area of tendon affected in each case seemed to be extremely small—the greatest length of tenderness in any particular tendon being apparently about ¼th inch. Examination at hourly intervals throughout the day showed that these tender areas were not constant, portions which had been tender at 8 a.m., for instance, not being so at midday, whilst others had at that time become first stiff and then tender, the new tender area being equally clearly demarcated. About six o'clock some increase in joint fluid was detected in the knee-joint, although the pain was less than it had been in the morning. The fluid increased progressively for a few hours and then remained constant during the next day. Throughout this period he described the knee-joint as painful, although the focus of this pain was found to be located in the tendinous junction of the quadriceps muscle with the patella (a common site). After this the fluid gradually dispersed, then the pain, and lastly the stiffness and creaking, in the inverse order of their appearance. Subsequently both wrists swelled, the sequence of events being exactly similar to that already described. The tendon sheaths principally affected were those of the superficial layer of the flexor surface where they pass beneath the anterior carpal ligament.

Subsequently all patients with pain and swelling of the joints were closely observed and as the result of these observations it is thought that the arthritis of rheumatic fever is a secondary phenomenon arising by direct extension from a primary tenosynovitis of the muscle tendons which surround the joint. This will explain the almost invariable experience that joint fluid from such cases is sterile. In the case of the knee-joint there may be a direct connexion between the tendon sheath and the joint cavity *via* the supra-patellar bursa, and this may account for the temporary lessening of the pain which is not uncommon whilst the joint cavity is filling up, since the tenderness and pain in the tendons following the period of creaking is no doubt due to the tension of the inflammatory fluid at that point, and its relief will therefore depend on it being able to disperse either along the sheaths or into the joint, where this is possible, before natural resolution starts.

The commonest sites for these initial areas of tenderness round the larger joints appeared to be: (a) In the wrists—any of the tendons might be affected; the tender areas were, however, always in the neighbourhood of the surface markings of the carpal ligaments under which they pass. (b) In the knees at the junction of the quadriceps tendon with the patella, and on the tendons on the internal aspect of the joint and in the semi-tendinosus tendon posteriorly. (c) In the ankles; over the tendons of the peroneus longus and brevis on the outer aspect, and the tibialis posterior on the internal aspect—as they hook round the malleoli. (d) In the elbows on the flexor aspect, not infrequently in the biceps tendon: this is not inserted very near the joint, nevertheless this lesion is subjectively interpreted by the sufferer as joint pain, and no doubt any subsequent inflammatory effusion into the joint cavity might take place by direct extension of inflammation from this tendon sheath to the synovium of the joint.

To recapitulate, the analysis of some forty cases of rheumatic fever showed that two stages precede the actual swelling of the joints. First, a feeling variously described as tension, stiffness, or creaking, referred to the joint. There is disinclination to move the joint, sometimes interpreted as "weakness." This lasts from 2–24 hours, and probably represents a condition of progressive swelling of certain tendons or their sheaths around the joint. The second stage is that of pain, originating in one or more points tender to pressure, and mostly situated in or over the larger tendons. This pain is largely referred over the joint, and is spoken of by the patient as "joint pain." It is probably due to an increase in tension due to localized effusion in the tendon sheath, and each area remains painful for 5–48 hours. Swelling can often be palpated at this stage along these areas. These points of tenderness are quite definite and discrete, and there may be a number of them round a single joint. (The pain can be abolished at each by an injection of procain.) The third stage is that of actual effusion into the

neighbouring joint cavity either from primary affection of the synovium of the joint, or quite often by secondary extension from that of the affected tendons.

#### (c) CARDIAC LESIONS (ASCHOFF NODULES)

No opportunity of studying this manifestation of the disease arose in the present series. Their occurrence in established cases of rheumatic heart disease and their histological structure is, however, well recognized. A subcutaneous nodule from the elbow, one of many which developed in the course of a severe first attack of rheumatic fever in a native boy, was removed and its structure was reported to be indistinguishable from that of an Aschoff nodule (Dr. F. Marsh).

It is suggested as the result of these observations that in rheumatic fever the general pyrexia and malaise and the local synovitis of tendons and joints which occur early are principally due to a non-specific reaction to infection such as may occur temporarily in the course of several other febrile diseases—e.g. scarlet fever or Malta fever. True subcutaneous nodules, however, are evidently reactions to a more specific process, and are evidence when they occur that this is beginning to predominate, and consequently that the prognosis is becoming graver. It is thought that Aschoff's nodules in the heart may be of the same nature and significance as these; their special importance lying only in their localization in a "vital organ."

Even in "benign" attacks of rheumatic fever in which these specific manifestations do not occur it seems probable that the initial symptoms (which it is suggested above may be largely non-specific) may become intensified and "fixed" by the specific agent, the prognosis probably varying with the degree of this action.

#### Clinical Types of Rheumatic Fever

Three types were met with and will be discussed separately: (1) The classical type. (2) A benign type. (3) Classical type which merged into chronic fibrositis.

The classical type, with general fever and peripheral tendon lesions leading to joint swelling as described, needs only brief further reference here. Two cases of permanent cardiac damage occurred. There was seldom much difficulty in diagnosis, and if they had not recovered within six weeks they were generally sent home, as it was considered that even after recovery they would be liable to relapses. A differential diagnosis which sometimes offered difficulty was undulant fever.

#### "ACUTE FEBRILE MYALGIA"

A benign form, for which the name "acute febrile myalgia" is suggested, and which it is believed as the result of subsequent experience will be comparatively common if looked for. It should not be regarded merely as a "mild" attack of rheumatic fever, since this diagnosis as commonly employed

implies that the myocardial damage may be progressive although the signs and symptoms are outwardly mild. Cardiac damage does not appear to follow this form at all. It responds well to salicylate therapy. In this form it is probable that the non-specific element is maximal and the specific factor (whatever it is) minimal. The onset of the attack is the usual one in rheumatic fever—malaise, pyrexia, sweating, fleeting muscular pains. The pyrexia is sometimes less in evidence than in normal attacks, however. After the first twenty-four hours there is also very little malaise, although pain and, later, swelling remain severe. The blood sedimentation rate is considerably raised, but is generally approaching the normal again (as is the patients general condition) in about a month. In these cases there was no previous history of rheumatism, although there was always a history of preceding illness and/or exposure or strain which had "pulled him down," as in the case of the classical attacks described above. As in these cases, the preceding illnesses were of widely varying types, and appeared to act by lowering the resistance of the patient to the attack of some more specific organism. It suggested that those cases may represent the attacks of the specific organism of rheumatic fever on a soil of unusually high resistance temporarily lowered by certain preceding factors.

The reason for separating this type as a clinical entity from rheumatic fever proper lies principally in its apparently benign (non-toxic) course. In nearly all the cases observed the patient was well and B.S.R. normal again within a month; and no sequelae, cardiac or otherwise, were observed four months later (except in one case in which some fibrositis persisted). No relapses were reported. The prognosis in subacute rheumatic fever is rightly regarded as so charged with malign possibilities that it seems important to recognize that a benign form may exist. The natural tendency of the medical officers in charge of these cases was at first to take the usual grave view and to recommend that they should be boarded out of the Army. It was chiefly the fact that the men themselves seldom thought seriously of their condition after 24 hours, but merely reported sick with an account of some muscular pain or joint swelling, that led us ultimately to modify our own view. The name (benign) "acute febrile myalgia" accurately describes the syndrome, and will emphasize the difference in prognosis from acute rheumatic fever of normal type, although these cases must not be confused with "acute epidemic myalgia" since no epidemic factor is present.

Even within the framework of this syndrome considerable variation in severity was found to occur. At one end of the scale was the patient who suffered with tonsillitis accompanied by mild fleeting arthralgic pains, which persisted for a longer period than usual after the throat infection had subsided and whose B.S.R. also remained raised. Such patients are unlikely to be admitted to hospital in civilian life, but are probably frequently seen by the

family doctor. At the other end of the scale the condition will merge into the classical type of rheumatic fever and the line of demarcation may prove difficult to determine. The features indicating these cases to be of the benign type seem to be (a) the short initial period of pyrexia and the patient's subjective feeling that he is not very ill; (b) the subsidence of the B.S.R. within a comparatively short period; and (c) freedom from tachycardia during early convalescence. It would probably be wise in civilian practice to take an electrocardiographic tracing in addition before deciding that the case was definitely of the benign type.

#### *Some Illustrative Cases*

A few typical summarized case histories of patients with "acute febrile myalgia" are quoted below. All of these men were returned to their units in about a month, and when followed up four months later were reported to be perfectly fit. It would seem therefore that the distinction made here between acute rheumatic fever and "acute febrile myalgia" is at least as useful clinically as that commonly drawn between acute typhus fever and its milder form of Brill's disease, or between smallpox and alastrim.

*Case 1.*—I. J. Age, 22 years. Service, 2 years. No previous personal or family history of rheumatic troubles. At time of attack was in poor health owing to a recent attack of bacillary dysentery, followed by chronic streptococcal furunculosis. No sore throats. In peacetime was law-student. Athletic. Unmarried. Plays hockey twice a week. Woke up one day after last match with stiff and somewhat swollen wrists and ankles. Difficult to walk, and was put on to light duty for two days. These symptoms cleared up, but as knees were also getting stiff and patient complained of sharp pains in neck and shoulders was admitted to hospital with temperature of 100.6° F.

Lightly-built wiry man with good appetite. Did not feel ill, but now complained of pains in quadriceps and wrists. No joint swelling. N.A.D. on clinical examination. Temperature 99° F. for first two evenings. B.S.R. 21 mm. Hb. 76 per cent. C.I. 0.9. W.B.C. 3,950 per c.mm. Sod. Sal., gr. x, tds. Uneventful recovery. B.S.R. 2 mm. on twenty-first day after onset. Returned to unit four weeks after admission. Subsequently had further attack of furunculosis, but no recurrence of rheumatism.

*Case 2.*—K. L. (R.A.). Age, 33 years. Service, 2 years. No previous or family history of rheumatic troubles; married, two children. In civilian life was decorator; worked outside in summer only. No previous illness since measles and whooping-cough in childhood till dysentery (Flexner) on arrival in Middle East six months previously. This was "cured" in hospital, but he had had diarrhoea since and had not felt well. No sore throats. Woke up one morning with synovitis right knee. Next morning pain, acute round both ankles but no swelling; "went sick" and was put on light duty. Next day other knee painful and also both shoulders and back. Did not feel ill at any time, but T.=101° F. Admitted to and seemed well in c.c.s. No temperature third day, so discharged

on fourth day; but relapsed four days later with pain in knees and admitted to hospital.

Healthy looking patient with good appetite. Said he felt well but rather tired, and had sweated last two nights. Nothing abnormal discovered except that movements of right shoulder and elbow were restricted and painful. Urine normal. B.S.R. 12 mm. T.=100° F. Blood count normal. The following is a chart of the tempera-

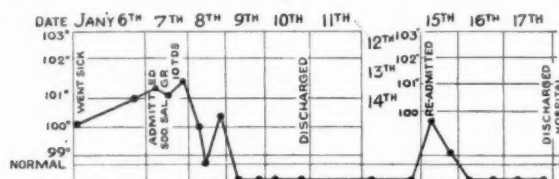


CHART 2.

ture during both attacks. On Feb. 3 (3 weeks later) there was no pain or stiffness anywhere. B.S.R. 3 mm. One month later "is doing full duty and feels very well." B.S.R. 5 mm. Four months later no recurrence.

Case 3.—M. N. Age, 27 years. Service 3 years. No personal or family history of rheumatism. Married, one child. "All children's diseases," "pleurisy" when 10 (bed 1 week). No sore throats. Non-venereal urethritis 18 months ago; cured. Depressed and not up to mark for last month. Woke up on morning of Dec. 21 with severe pain in both thighs, made worse by movement, and palpitations. That day he joined in a three-day "exercise" under rough conditions and sleeping in open with snow on ground. On his return his left knee was swollen, hot, and red, and he had severe pain in both hips and buttocks. He was admitted and next day both wrists also painful, but B.S.R. only 3 mm. (Dec. 28). B.P. 120/70. Slight systolic murmur at apex of heart. By Jan. 1 he still had stiffness of elbows, but did not feel ill. B.S.R. 10 mm. On Jan. 28 B.S.R. 3 mm.; murmur gone. Feels very well. Discharged. An electrocardiogram was subsequently done and reported as normal. On enquiry at end of April his M.O. stated that he was perfectly well and doing full duties and murmur had not reappeared.

The following typical cases are more briefly summarized:

Case (a).—O. P. Age, 25 years. (A very mild case.) Severe tonsillitis, and developed slight pain in right patella region on second and third day. On third day his temperature was 100° F. and right knee slightly swollen. On fifth day throat well and temperature normal, but B.S.R. 17 mm. and pain in left shoulder. On sixteenth day felt well, but B.S.R. was 26 mm. On twenty-seventh day the B.S.R. was again normal (9 mm.) and patient had had no further pains and resumed normal work.

Case (b).—Q. R. Age, 23 years. No previous rheumatism. On Dec. 5 caught a severe cold, which was followed by pains in knees and swelling of ankles. Next day pain at bottom of back and round right hip, which kept him awake. Slight sore throat and temperature 101° F.; he was febrile for four days, this being highest temperature reached. Pulse rate, 100. Heart normal. Dec. 9 was admitted, as both knees and ankles swollen and painful. No fluid in joints. B.S.R. 18 mm. Put on to sod. sal. gr. xx tds. Next day temperature and pulse normal. W.B.C. 8,000 per c.mm. (77 per cent. polymorphonuclears, 21 per cent. lymphocytes). On Dec. 14 seemed very well. B.S.R. 1 mm. On Dec. 19

returned to his work. Four months later reported "very fit."

The following case is of interest as the resistance appeared to be lowered and the disease activated as the result of T.A.B. inoculation, and not of illness.

Case (c).—S. T. Age, 22 years. No previous rheumatic or other illness. Very occasional sore throats during last few months. Ten days previously was vaccinated and given routine T.A.B. injections and had felt seedy since. Sudden onset of pain in both shoulders going round to upper back, knees, and right ankle; T.=101° F. Pains disappeared and temperature was normal after two days of sod. sal. (gr. 120), but B.S.R. 35 mm. After first twenty-four hours in bed felt quite well. Eight days later B.S.R. 5 mm., and after thirteen days was discharged. Four months later reported perfectly fit and doing full duty.

Case (d).—"Benign" rheumatic attack provoked by burns. Italian soldier aged 22. Admitted Nov. 2 with superficial burns both lower limbs. These had produced considerable shock. T.=102° F.; P. 100; R. 20. No malaria. Two days later onset sudden acute pain both legs during night and much sweating. T.=102° F., P. 70. Very restless and in much pain next two days—chiefly right hip (which he could not move) and both knees and wrists swollen. B.S.R. 58 in 1 hour. Sweating constant. Much better in another two days and didn't feel ill. Left knee still swollen. Burns healing. Nov. 15 no further pains or swelling.

Case (e).—U. V. Age, 25 years. This case would seem to have been provoked principally by unaccustomed exposure (as were several others). No personal or family history of rheumatism. Sore throats for two to three days each year for last five years; not this year. Sleeping in open on right side in intense cold. After two weeks of this woke one morning with pain right hip and knee, which later swelled up. Did not feel ill but was admitted. Temperature 99° F. Slight increase in joint fluid of right knee. B.S.R. 58 mm. Pyrexia lasted only for two days, and after two weeks B.S.R. was 21 mm. and only slight stiffness remained. Three weeks from admission B.S.R. 3 mm. and patient seemed absolutely fit and was discharged.

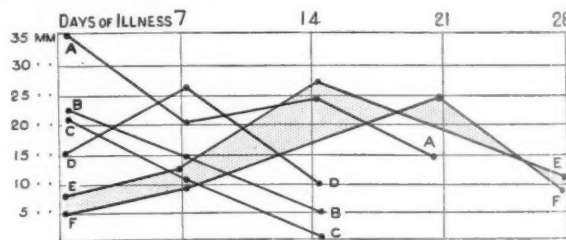


CHART 3.

Charts of the B.S.R. in 6 typical cases of "acute febrile myalgia" showing that in most cases this has resumed a normal level a month after onset of the attack.

Cases E and F show a common form of "lag" curve; the B.S.R. not starting to rise until well after the onset of the disease. This type is generally normal again about a month after it starts to rise.

To summarize, it is suggested that a benign form of rheumatic fever exists which is not uncommon and for which the name "acute febrile myalgia" is

proposed, in order to avoid the implications attaching to the diagnosis of ordinary rheumatic fever. The onset is similar to that of the classical attack, but fever rarely lasts for more than 48 hours. It responds to salicylates. The patient rarely feels ill after the first two days, and the blood sedimentation rate returns to the normal in about a month (see chart). There are no cardiac or other sequelae.

#### CLASSICAL TYPE MERGING INTO FIBROSITIS

It was noticed in several cases that the acute attack instead of resolving gave place to chronic muscular pain and stiffness from which the patient was seldom entirely free. This seemed to occur equally after primary attacks as after relapses. These patients also became unduly sensitive to exposure and to muscular strain, and they generally appeared unlikely to return to a high army category. Later a neurotic element was sometimes added, but this appeared to be the effect and not the cause of the chronic pain. The psychiatrist was asked to examine several cases and agreed in general with this conclusion.

The rheumatic attack which runs this course is often clinically not a severe one and none developed cardiac complications. It was noted in those cases which resulted from relapses that the primary attack had occurred after the age of 15 or 16; that is at a rather later age than is usual. Several of these cases are reported in full below.

#### RHEUMATIC FEVER AND CHRONIC FIBROSITIS

It is common experience that patients are not infrequently seen with chronic fibrositis which they attribute, apparently rightly, to an attack of rheumatic fever. In view of the lack of certainty regarding the specific causative agent of the latter, and our almost complete aetiological and pathological ignorance regarding fibrositis, no authority has publicly connected the two diseases. Detailed history, taking in such cases as have given a story of this type has, however, served to show that the two diseases may in certain cases stand in the relation of cause and effect. This can be shown by recording one or two such cases in full.

*Case X.*—Age, 29 years. Service  $2\frac{1}{2}$  years. Category A1. (A first attack of acute rheumatic fever leading to chronic fibrositis.) Father suffers with severe muscular rheumatism in his shoulders. Mother, no special history. No illness except whooping-cough and measles when about 10 years old. No previous rheumatism. Was a solicitor's clerk in peacetime. Unmarried. One year before admission had a carbuncle on left leg and was in hospital nine days. In the next two months (March and April) this occurred on right leg and recurred after healing. In December a similar lesion appeared on the left chest wall, and just as that was healing another turned up on right side of neck (haemolytic streptococcus). At this time he began to complain of pains in legs and lower back. Later his feet became very painful and he could hardly walk. He felt "washed out" but not really ill; could not eat much. No headache. He was admitted to hospital with  $T. = 101^{\circ} F.$ , and this rose to  $103^{\circ}$  soon afterwards. He still did not feel very ill,

but the pain in the legs and arms was severe enough for three nights to prevent consecutive sleep. On the first night he sweated profusely, and after this the pain moved to the shoulders for a time.

On examination he was a rather pale but well-developed man, with injected conjunctivae. Tongue heavily coated. Liver and spleen not felt. All usual tests for specific infections were negative. Urine, normal. He had a healing boil on right side of neck, but no adenitis. Throat, normal. Knees and ankles very swollen owing to effusion: sodii. sal. gr. xx, t.d.s. On the evening of the sixth day after admission the temperature was  $100.6^{\circ} F.$ , and this ended his pyrexia, which had ranged between  $99^{\circ}$ – $103^{\circ} F.$  He felt much better, but fairly severe pains still flitted between his legs and shoulders. The boil had healed, and no joints were swollen, although the knees were still very tender. The heart appeared to be normal. B.S.R. was 10 mm. (Westergren). Three weeks after admission he felt well and continued afebrile. There was, however, severe pain in the left shoulder, chiefly the deltoid region, and this was worst in the mornings. The B.S.R. was 2 mm. and his Hb. 94 per cent. W.B.C. 8,000 per c.mm. (polymorphs 45 per cent.; lymphocytes 43 per cent.; large mononuclears 7.5 per cent.; eosinophils, 3 per cent.; and basophils, 1 per cent.). The pain remained in the shoulders and sometimes the neck, but he made an otherwise uninterrupted recovery.

He was seen two months later and still complained of these pains, which he said were unchanged. Examination showed the presence of typical fibrositic "myalgic spots," which were extremely tender and the source of the pains he complained of. He was otherwise well and heart was normal. Four months later the report stated that he was exactly in the same condition, with the additional fact that he was now extremely sensitive to draughts and wet weather, both of which factors would provoke severe pains in his shoulders and neck.

*Case Y.*—Aged 22 years. (A case of juvenile rheumatic fever with one subsequent attack and subsequently a gradually progressive condition of fibrositis becoming established.) Father (a plumber) often suffers severely, his joints swell, and he has to go to bed during attacks. Patient's paternal grandfather died of "rheumatic heart disease." His mother's side of family showed no case of rheumatism. His sister aged 20 complains frequently of severe pains in shoulders. The patient is also a plumber in a dockyard and frequently gets wet through. After this, with an interval of 1–2 days, during which he feels no harmful effect he generally has to spend several days in bed. He has two young children who are not rheumatic. His only other sickness has been measles as child and pleurisy (bed 2 weeks) aged 12. He started work at the age of 15, but after 2 months was taken ill with rheumatic fever, which kept him in bed for 6 months. The attack started gradually with "growing pains" which progressively got worse and spread from legs to arms and shoulders. Medicine did not help, and he developed fever and sweated at night heavily. (He volunteered the statement that the sweat had a pungent smell.) He states that he came out in crops of subcutaneous nodules on knees, wrists, and elbows, "which interested the doctor" but which were not painful or tender. They were of sudden onset and each crop lasted about 2 weeks. He felt very ill during this period, and said that it was agony to move arms or legs, and the joints were padded with wool.

At the end of March, after 2 weeks convalescence on sod. sal. and ultra-violet light he gradually recommenced work, and had resumed full work in April, the onset of the attack having been in August. He appeared to

have completely recovered until the following September, when he noticed twinges of pain in his shoulders after carrying heavy lead pipes. Two days rest and sod. sal. did not help, but they gradually passed off. Since then attacks of this sort have occurred every 2 to 4 weeks, and prevented him working for 2 or 3 days owing to the pain in shoulders and knees. Does not generally have to go to bed unless these are the result of a wetting. At the onset of the war these attacks were becoming more severe and lasted up to 7 days. He had joined the Territorial Army in 1938, and was called up without medical examination at outbreak of war. Since then had another attack of rheumatic fever in Army, which was not nearly so severe as his previous one and lasted only a month. He managed to carry on in a sedentary employment in England (and was in fact better than he had been in peace time), but on the voyage the pain became very bad, and since arrival in the Middle East he had spent most of his time in hospital (Dec.-March).

On examination he was a rather pale and slightly-built man. No abnormalities discovered other than fibrositic "nodules" around buttocks, sacrum, lumbar region, and shoulders. Many of these were extremely tender, and the pressure on these would refer the pain widely and reproduce his "attacks." No pyrexia. Heart, clinically normal. Blood count normal. Urine normal. B.S.R. 8 mm. Electrocardiograph: slight prolongation of P-R interval. Procaine injection of tender nodules produced improvement, but other spots subsequently appeared to replace these, and no permanent cure by this method seemed to be possible. He was re-graded and given a sedentary job again, in which he found himself able to carry on.

*Case Z.*—Age, 32 years. (A case of chronic fibrositis of 12 years' duration, dating from an attack of rheumatic fever and exacerbated by an attack of "acute fibrositis" lasting three weeks a year later.) Mother is practically a cripple with rheumatism. Father died young. Patient had no rheumatism as child, nor had his sister. No previous illness. He started work in a shipbuilding yard when 16—most of the time up to his knees in water. After a few months of this he began to contract sore throats and colds at very frequent intervals, often laying him up for many days at a time. Latterly he had several attacks of bronchitis. At the age of 20 he had a sudden attack of rheumatic fever in January, with pyrexia, sweatings and hot painful joints. He was in hospital for 6 weeks and felt very ill. He resumed work in the summer, but was conscious of tender spots in his back and shoulders, and he suffered with occasional slight attacks of generalized muscular pain. These have subsequently persisted. In March of the next year the mild pain in his back became intense and spread, and he was again in hospital for 3 weeks. He was pyrexial only on the day of his admission, and did not feel very ill at any time. The condition responded to treatment and he returned to work under his previous conditions. He was able to continue with this until the outbreak of war without interruption, except for a period every winter during which the pains in the back and shoulders became exacerbated and he had to retire to bed and be treated medically for a few days. A few years ago he broke his leg and clavicle in a cycling accident, and he has noticed that "rheumatism" has also settled down at these sites, although the alignment seems to be perfect.

During the last 3 years—in the Army he has been in an indoor job and has managed not to go sick in spite of several sore throats. He was seen as an out-patient on account of the pains in the back which still persisted.

On examination looked healthy and the heart appeared to be normal. Many "myalgic spots" which were acutely sensitive to pressure were found along the edges of the trapezius, rhomboid, and lumbar muscles. The blood count and the B.S.R. were normal. Injection with procaine into these spots appeared to relieve the condition very considerably, and he returned to his work.

#### COMMENT

From a study of these and similar cases one is struck by the clear-cut nature of their history. From this it appears reasonably certain that the fibrositis, from which they now suffer, dates its origin from the first attack of rheumatic fever, and it is often rendered more chronic by a second attack. There seems little doubt that these attacks were genuinely of rheumatic fever, and the definite family history of rheumatism in each case is noteworthy.

There does not seem to be any suggestion that it is "chronic rheumatic fever" rather than fibrositis from which these patients are now suffering, since in the cases quoted the patients were well in themselves, no cardiac lesions had developed, and the temperature and B.S.R. were normal. It was also in all cases the soft tissues and not the joints which were affected, except during the original acute attacks. The "trigger points" and the distribution and reference of the pain are now typical of chronic fibrositis. There seems, therefore, no reason to differentiate this end result from fibrositis of other aetiology. It is submitted that this view is rationalized by the ideas as to the basic nature of rheumatic fever which have been put forward earlier in this paper.

It has been observed elsewhere (Copeman, 1943) that certain areas of the body in susceptible people can be rendered prone to fibrositis as the result of attack by one of several of the common fevers, and that if reactivation by these or other infections occurs before resolution has taken place the condition will become chronic. The aetiology of chronic fibrositis in these cases, although infective, is not therefore a specific one. Acute fibrositis indeed seems to be a common temporary host reaction to many separate types of infection, and will sometimes persist. In the case of rheumatic fever it seems possible that it is this non-specific element of the fever which initiates the disease and a specific rheumatic factor which later intensifies and prolongs the process in certain cases; and which will in time presumably also produce cardiac lesions. The prognosis would seem to depend upon the speed and dosage in which this specific factor follows up the attack of the initiating non-specific factor. In the cases described of "acute febrile myalgia" the appearance of the specific factor would appear to be sufficiently delayed to enable the patient (whose normal resistance is high) to establish adequate defence. It might therefore be regarded as the clinical link between acute rheumatic fever and chronic fibrositis. In debilitated patients—i.e. those in whom resistance is normally low (or in whom the "dosage" of "preceding factors" has been high)—the disease

will run its classical course, the specific element blending from the start with the initial non-specific febrile fibrositis which seems to be the basic element of the disease.

#### Summary and Conclusions

An exceptional opportunity was presented for studying the natural history of rheumatic disease in a body of healthy young adults who were isolated from civilized environment for a considerable time in a remote desert. Later, other unusual opportunities arose for studying certain cases of acute rheumatic fever.

It is generally agreed that acute rheumatic fever shows unmistakable signs of being a specific infection. It was established, however, that the possibility of an external source of infection being the cause of the 32 cases suffering with first attacks and 10 cases who had had previous attacks in peacetime was remote. The possibility that the specific infective organism might have been able to lie dormant in the tissues of apparently healthy hosts is therefore examined.

The nature of the infecting organism of rheumatic fever is discussed in the light of clinical experience, and a suggestion is offered to explain the common association of the streptococcus in temperate climates.

The infection gave no evidence of being spread by droplets except in one small series which is described.

It was observed that preceding factors were present in almost every case of acute rheumatic fever, were of two types, and that both were generally operative: (1) A non-rheumatic infection whose role appeared to be to lower the patient's general resistance. This possibly allowed of a successful attack by the hypothetical specific organism. These "preceding infections" were not always streptococcal in type, but comprised the diseases such as dysentery, sandfly fever, and even malaria, which are most commonly met with in the country of observation. (2) A physical factor which comprised chiefly cold, wet, or fatigue in unaccustomed "dosage." A small series of cases is reported in which physical factors in extreme degree appeared to be alone responsible. In a series of cases seen in Malta soon after the siege it is probable that malnutrition was also a factor.

An attempt was made to arrive at the essential nature of rheumatic fever from close clinical observation of this series of cases. Every case showed: (1) General signs and symptoms, such as are common to most general infections. (2) Local signs

and symptoms which comprise muscle and tendon stiffness and pain leading to joint stiffness, swelling, and pain. It was thought that even these symptoms and signs were possibly not in the first instance due specifically to rheumatic fever, but to a non-specific "fibrositic" process (possibly secondary to the fever): the arthritic process arising secondarily by direct extension from this. Cases of true rheumatic fever will, however, show later the specific "stigmata" of subcutaneous nodules and cardiac lesions in addition. It is suggested that these two specific lesions are of similar nature as regards their morbid anatomy.

This view leads to the conclusion that acute rheumatic fever is basically an acute febrile and progressive form of fibrositic reaction occurring in localized areas of tendon sheaths adjacent to joints. The "joint pain" complained of appears to be really referred from these areas, and later, when effusion occurs in the joints, it is generally a secondary extension of the inflammatory process from the affected tendon sheaths, and not a primary arthritis of blood-borne origin. It is only when the specific element comes into the picture in sufficient "dosage" that the condition becomes differentiated from the polyarthritis which may occur as the result of other types of infection such as the gonococcal or meningococcal. (A method of estimating this specific factor would determine prognosis more accurately than will clinical observation alone.)

Three clinical types of rheumatic fever were observed: (1) The classical type, which ran its accustomed course. (2) A "benign" type which has not, it is believed, been previously described. This appeared to be non-epidemic, of short duration, and probably not uncommon. For this syndrome the name "acute febrile myalgia," is suggested. Typical case-histories of patients suffering with this type of disease are recorded. (3) The classical type which, instead of resolving, appeared to merge into a condition of chronic fibrositis, which was shown to be difficult to differentiate from fibrositis arising from other causes.

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## ASPECTS OF "FIBROSITIS"

BY

F. A. ELLIOTT

The conception of fibrositis, introduced in its present form by Sir William Gowers in 1904, provided so ready an explanation for a number of otherwise knotty problems that it was and is widely accepted as a disease, although it has never been placed on a satisfactory pathological basis. It is true that Stockman, Brogsitter, and others have found non-inflammatory fibrotic changes and endarteritis in the subcutaneous and myo-fascial tissues, but the changes have been slight and—if we except the case of panniculitis in obese women—their relation to symptoms indefinite. The scepticism born of this pathological ambiguity is increased by the circumstances that many conditions formerly viewed as typical examples of fibrositis are now known to have other cause. Many cases of lumbago, sciatica, and "brachial neuritis" (Semmes, *et al.*, 1943; Spurling, *et al.*, 1944; Elliott, *et al.*) are due to prolapse of the nucleus pulposus at the appropriate level. Other cases of lumbago are examples of spondylolisthesis, or the reverse condition of posterior displacement of the fifth lumbar vertebrae—conditions which depend for their recognition on improved x-ray technique. Orthopaedic surgery has demonstrated the importance of postural strains in the production of pain in the limb girdles and back. These advances have greatly reduced the number of cases in which it is necessary to invoke a hypothetical inflammation of fibrous tissues, and it is probable that this trend will continue. Nevertheless, it is still a common experience to find that cases of spondylitis, prolapsed disc, spinal tumour, and so on, have been treated as fibrositis by clinicians who are fully aware of these other diagnostic alternatives. It has appeared to me, from a review of personal mistakes of this kind, that among the factors which contribute to this confusion the most outstanding is the misinterpretation of tenderness as a physical sign. It is the purpose of this article to make some general observations on this topic, with special reference to muscle tenderness.

### Diagnostic Criteria for Fibrositis

Modern literature emphasizes four points in the diagnosis of fibrositis: local tenderness, reproduction of symptoms by pressure on the tender points, the presence of nodules, and the cure of symptoms by the injection of procain into "trigger areas." A critical scrutiny of these criteria at once reveals certain pitfalls.

In the first place, it is not possible to map the distribution of tender spots by palpation alone, for it is a matter of simple physics that, since tenderness is elicited by pressure, it will be most easily found where there is something firm, like bone or ligament, to give counter-pressure to the exploring finger. Current descriptions of the common sites of "fibrositic" tenderness are for this reason unreliable, as can readily be demonstrated by exploring the tissues with a needle.

Secondly, tenderness found by palpation does not discriminate between superficial and deep tissues, so, unless special measures are adopted, the clinician is prone to attribute any tenderness he may find to the tissues he expects to find it in. Cutaneous hyperalgesia must be excluded by testing with pinprick. Subcutaneous tenderness must next be tested for by pinching up a roll of skin between the fingers, and is valid only if cutaneous hyperalgesia is absent. Tenderness in the deeper tissues is more difficult to judge and may require needling for its precise location. That these are not merely theoretical considerations may be illustrated by three cases, in all of which there was tenderness in the region of the sacro-iliac joint. One had an epidural abscess at the level of the third lumbar vertebra and the tenderness was of the skin, which here received fibres from the descending branch of the third lumbar nerve. The second had a prolapse of the fourth lumbar disc, irritating the fifth lumbar nerve, which supplies the gluteus maximus—the site of the tenderness. The third had tenderness deep to the myofascial strata, located by needling, and was due to a tuberculous lesion of the sacro-iliac joint. All three had been regarded as cases of fibrositis because they had lumbago with a circumscribed area of local tenderness as described.

The third pitfall in the interpretation of tenderness is by far the most important, both practically and in its physiological implications. It is wrong to assume that local tenderness is necessarily due to local disease. In only one of the above examples did the tenderness indicate the site of the primary mischief. Tenderness means a reduction in the threshold for pressure pain. It implies an amplification of the response to pressure, and the process responsible for this amplification may be situated at any point in the sensory pathways, between the nerve endings in the tissue palpated and the thalamus. (For present purposes the tenderness which accompanies lesions in the spinal cord and thalamus will

be excluded from the discussion.) Tenderness of the calf muscles may be due to local injury or local fatigue; but similar tenderness may be found when the responsible focus is an irritative lesion of the sciatic nerve, such as a gunshot wound in the thigh. It may be due to a root lesion, such as that caused by a prolapsed disc, or a tumour of the cauda equina. Local tenderness should not be accepted as proof of local disease unless there is satisfactory collateral evidence of a lesion in the area palpated. Even such evidence may be misleading, for it sometimes happens that some old-standing lesion such as a scar, or a joint injury, may become tender, and appear to be the source of pain by reason of its fortuitous presence within an area of referred tenderness from an irritative lesion of a nerve or nerve root. This fact, besides having interesting physiological implications, is clearly of practical importance and underlines the need for care in the elimination of central causes of tenderness. It can no longer be argued that the rarity of root syndromes reduces the importance of this observation. The advent of the prolapsed disc in clinical medicine has changed all that.

It is held by many that if the infiltration of procain into tender spots or nodules removes the patient's symptoms, the diagnosis of fibrositis is confirmed. This is not always true. I have pointed out (Elliott, 1944) that complete relief may be obtained by this measure when the tenderness is due to prolapsed discs and spinal tumours. Partial relief is more common in such cases, but whether partial or complete it is a paradoxical phenomenon. That it is susceptible of rational explanation will appear below. The practical issue is that a positive "novocain test" does not exclude a root lesion.

The fourth point stressed as diagnostic of fibrositis is the presence of nodules. But this, too, appears to offer practical difficulties, if we are to judge by the cases of spinal tumour and related conditions in which nodules have been found by competent observers in the early stages of the disease. The normal granularity of the subcutaneous tissue, and the coarse fascicular arrangement of some muscles are readily misinterpreted, particularly when they are tender. Biopsies have revealed many things: lipomas, neurofibromas, equivocal fibrosis, hyaline changes in muscle, and more often nothing at all. A striking instance of the last was a girl who had a tender nodule the size of a broad bean in the upper free edge of the trapezius. It was hard, and varied in size from day to day. She was given a general anaesthetic and the lump disappeared; an extensive search in the subcutaneous muscle, and submuscular layers revealed nothing amiss, and the lump never recurred. The virtue of this case lies in the fact that the nodule was visible as a hump under the skin, as well as being obvious to palpation. It appeared likely that the mass was due to spasm of muscle fibres in the trapezius, and it led to a series of observations on muscle tenderness which have produced new facts relevant to the problem of fibrositis. These will be outlined.

### Muscle Spasm and Tenderness

In the first instance attention was confined to the tenderness of muscle occurring in proved root lesions. The site of the tenderness was established by differential testing. The traditional view of such hyperalgesia is that the impulses generated by palpation are normal impulses, but that they get amplified at some undetermined level in the central sensory pathways because they ascend *via* an irritated root. A second theory is that the presence of a root lesion increases the sensibility of the peripheral sensory endings in the tissue palpated. This controversy is unsettled and need not be discussed here. The outcome of the present investigations is to show that within these areas of increased sensory excitability, however they arise, there is in some cases a corresponding increase in motor irritability: that is to say, the tender muscles are more irritable than non-tender muscles, and are sometimes the seat of involuntary spasm involving small groups of muscle fibres. Such spasm produces both pain and tenderness, and becomes a source of pain over and above that which comes from the root lesion.

The possibility that subclinical spasm might account for some of the pain in these cases of root lesions was entertained on clinical grounds. It was submitted to instrumental investigation because it could not be either proved or disproved by palpation. In the electromyogram we have an instrument capable of accurate assessments of muscle activity. Electrodes are inserted into the muscle through a hypodermic needle, so bringing them into contact with muscle fibres at the tip of the needle. The electrodes are connected through a high-gain amplifier to a cathode-ray oscilloscope fitted with a camera. There is no electrical activity in muscle when it is at rest, but as soon as it contracts there is a change of potential which can be recorded on the oscilloscope.

The application of this method to the tender muscles in root lesions has been fully recorded elsewhere (Elliott, 1944). It was found that the tender muscles were irritable, responding to palpation and needling with prolonged outbursts of involuntary activity, denoted by showers of action-potentials. At the most tender points there was in addition sustained motor activity which was not due to the presence of the needle, because in favourable cases it could be recorded from skin electrodes, and which lasted for several minutes at a time. It died away at once if procain was injected at the site of the discharge, and was abolished by a spinal anaesthetic. It occurred with the patient relaxed, and was obviously localized to a small portion of muscle, for by using a multi-channel recording system it was possible to take simultaneous records from tender and non-tender areas in the same muscle. Action currents came only from tender areas. Such particulate activity within a muscle which is otherwise at rest cannot be produced voluntarily and is thought to represent involuntary spasm. In radicular sciatica it has been recorded in tender "trigger"

areas in the gluteus maximus and medius, and in the calf. In radicular pain in the upper extremity it has been found in the trapezius, supraspinatus, triceps, and extensors below the elbow. These are muscles with an extensor function, a distribution which has been constant thus far and which coincides, be it noted, with the usual sites of "rheumatic myalgia." It has not been found in purely flexor muscles.

The presence of these motor phenomena in the muscle innervated by irritated nerve roots supplies a possible explanation for the relief from pain which sometimes follows the injection of procain into tender areas within the territory of the affected root. It may be supposed that the root lesion gives rise to painful impulses which reflexly stimulate the motor cells of the anterior horns, so producing contraction of the corresponding groups of muscle fibres. Such contraction, if sustained, would give rise to both pain and tenderness, so increasing the flow of painful stimuli into the spinal cord and thereby exciting more spasm. If the reflex arc be cut, either by the injection of procain locally, or by a spinal anaesthetic, the spasm should stop and the relief from pain would be immediate. The degree of such relief would depend on how much of the patient's discomfort came from the root lesion and how much from the secondary spasm. If the former had become quiescent—as such lesions do—the spasm alone might be responsible for the pain, and in such a case the relief would be complete. Whether this hypothesis is correct or not, the abnormal irritability and sustained spasm demonstrated by the electromyogram introduce a new factor in the interpretation of muscle tenderness.

The findings in sciatica and "brachial neuritis" due to prolapsed discs encouraged an extension of this work to other forms of muscle tenderness. On theoretical grounds, any adequate stimulus coming in to the spinal cord should produce these motor changes, whether the source of the stimulus lies in a root or not. It appeared likely that an inflamed intervertebral joint, for instance, might give rise to spasm in the related segment of the erector spinae. In default of a suitably clear-cut case an artificial lesion was induced in a normal subject by injecting hypertonic saline into the sensitive area surrounding the articulation between the first and second lumbar vertebrae on one side. Unilateral subclinical spasm was induced in the sacrospinalis while the pain induced by the injection was at its height. This has been repeated in the dorsal area, but is more difficult owing to the difficulty which normal subjects have in relaxing the muscles of this region and the correspondingly high incidence of artefacts in the records obtained.

In two cases of long-standing thoracic scoliosis of undetermined aetiology pain and tenderness were referred to the erector spinae on one side at the level of the greatest deformity. The muscle here showed increased irritability and foci of spasm. Similar findings have been reported in an important paper by Hassett and Denslow (1942), who have studied

postural strains in their relation to muscle fatigue. Failure to detect postural abnormalities will lead to an incorrect interpretation of local tenderness in such cases.

#### TWO CASES

Similar evidence of spasm has been encountered in two cases which correspond more closely to the traditional picture of fibrositis. The first was in a neurotic woman who developed acute pain and tenderness in the nuchal muscles, with occipital headache. She attributed it to sitting in a draught, but closer enquiry established that she had had a sudden severe "crick" in the neck while turning her head the day before. There was severe spasm in the nuchal group on one side, and a lesser degree on the opposite side. The head was held stiffly. Diagnosis here was a matter for speculation; but it was analogous to the lumbago of a prolapsed disc.

A second case was that of a woman, likewise highly strung, who suffered from periodical pain in the shoulders and neck. Two acute attacks followed the removal of septic teeth, and were accompanied by a temperature. There were numerous tender spots in the upper fibres of both trapezii, the levator scapulae, and the rhomboids. Pain was induced by movements of the neck which relaxed the affected muscles, and this pain was felt in the muscles and not in the neck. The tender muscles showed many areas of spasm. She was relieved by certain postures and by lying in a hot bath. It was difficult to avoid the conclusion that she had a localized arthritis of the cervical spine, with secondary spasm of the related muscles; but here again proof was lacking.

#### Some Factors in Muscle Pain

The factor of neurosis has been mentioned with a purpose. The incidence of muscle spasm has shown a direct relation to the severity of the local lesion and also to what may loosely be called the nervous constitution of the subject. It is more common in severe lesions than in slight, and in highly-strung subjects than in the phlegmatic. This is what would be expected if the presence of spasm depends, as postulated, on the establishment of a local reflex in the spinal cord. Facilitation from above will be greatest at moments of stress and worry—conditions which not only sharpen the perception of pain but also increase the reflex excitability of the nervous system. This is in accord with the known effect of such factors on "rheumatic" pains.

The part played by muscle pain varies from case to case. In many cases of prolapsed disc, for instance, there is no evidence of spasm, and the patient's discomfort comes from the local lesion, its effect on the posterior common ligament, and the nerve root. Even when spasm is present it makes a very variable contribution to the patient's total discomfort, as can be judged from the unpredictable degree of relief from the injection of procain and other substances. In some cases the amount of pain which arises from relatively small foci of spasm is remarkable, and in searching for an explanation for this two things have become apparent. The first is that involuntary and "unphysiological" contraction of skeletal muscle is immediately painful, as in the familiar case of cramps in the calf. This pain comes

on at once and is not dependent on the accumulation of the metabolic products to which muscle pain is attributed. It appears to be related to the distortion which is produced in a muscle when some of its fibres contract and others do not.

The second factor concerns the blood supply of the muscles. It is known that a reduction of the arterial supply to a muscle will bring about pain if that muscle is made to work, as in claudication. I have from time to time observed reduction and even temporary obliteration of the arterial pulsation at the ankle in the presence of severe sciatic pain; the foot has felt cold, but with rest and relief from pain the pulsation has returned to normal.

The clinically observed reduction in the blood supply to the limb has been confirmed by a thermoelectric study of muscle temperatures in subjects with root lesions. By using needle electrodes it is possible to record the temperature of the tissue in contact with the tip of the needle. This work is still proceeding, but it has been found that the tender muscles are "cooler" than those of the normal side, and that the distribution of this change shows that not all of it is due to disuse of the limb. The drop of temperature is especially marked in muscles which are the seat of spasm, and exceeds by far the limits of normal variation. Since the temperature of any tissue depends partly on its own metabolism and partly on the central-heating effect of its arterial blood supply, it follows that, if a muscle which is abnormally active is found to be cooler than inactive muscle in the opposite limb, the lowering of temperature must be due to reduction of blood supply. How this comes about need not be discussed here, but the fact that it occurs promises to be of importance in the study of muscle pain. In the present context the existence of a relative ischaemia supplies the conditions under which spasm of skeletal muscle is most likely to produce pain. Secondly, the existence of such ischaemia over long periods may prove a source of trophic changes in the tissues. The rapid wasting of muscles without a corresponding loss of power, which is so common in root lesions, may have a vascular basis. The rather equivocal fibrosis and endarteritis described by various authors as the fibrositic lesion may be the result of prolonged partial ischaemia. These studies are in an early stage of development and have not yet been extended to the wider field of non-radicular cases, but it appears probable that closer study of the vascular responses to pain in joints will prove worth

while. They are mentioned here only in the most general way, pending further work on the subject. It is felt that, no less than electromyography, they offer a profitable line of attack on the problem of chronic rheumatism.

#### Summary

We have seen that there has been a progressive reduction in the number of conditions which can be attributed to fibrositis, and that the application of a rigorous clinical discipline coupled with new technical methods threatens to continue the process of dismemberment.

The present work seems to show that, apart from a hypothetical inflammatory origin, muscle tenderness may have two explanations. The first is the traditional one—a central lowering of threshold to sensory stimuli. The second is the effect of localized involuntary spasm arising reflexly from lesions elsewhere. This spasm is accompanied by an increased irritability and occurs in extensor muscles which are anatomically or physiologically related to the site of disease. Thus a prolapsed disc in the lumbar spine may give rise to spasm in the lumbar muscles—that is, an anatomically determined spasm—and it may also cause spasm of small groups of muscle fibres in the buttock and calf by irritating the fifth lumbar root. Such spasm contributes a variable and at times considerable amount of pain to the patient's discomfort, and this may be relieved by measures taken to reduce the spasm. Such treatment is valuable, but it has been pointed out that the elimination of pain by local injections of procain does not necessarily exclude a central lesion of the nerve roots or spinal column.

This thesis does not seek to shut the door on fibrositis as a clinical entity, and it would be unfortunate if the hypothesis of myofascial inflammation were to be replaced, at this stage, by a facile generalization that muscle tenderness is always due to spasm of skeletal muscle.

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# A CASE OF TUBERCULOUS RHEUMATISM (GROCCO-PONCET TYPE)

BY

E. MONTUSCHI

The conception that rheumatoid (atrophic) arthritis and acute polyarthritis simulating rheumatic fever may in certain cases have a tuberculous aetiology with an allergic or bacillaemic pathogenesis, was born in Florence with the teachings of Pietro Grocco (1892), who held the chair of clinical medicine at the University.\* Because of this, many papers on tuberculous rheumatism were published in Italy at the beginning of the century. A second crop of papers in the 1930's can be traced to the fact that Cesare Frugoni, a disciple of the Florentine school, became Professor of Medicine in Rome at that time. In 1932 Frugoni and Peserico, reviewing the subject of tuberculous rheumatism, proposed that the condition should be named "Grocco-Poncet" rheumatism. They expressed doubts of the claims of Reitter and Loewenstein (1933) that a tuberculous bacillaemia is commonly found in this condition, and also rejected the claims of the French authors that the condition itself is very common. The Roman school of medicine adheres to the view (Klinge, 1929) that rheumatism is a specific reaction of mesenchymal tissue to non-specific noxae, and believes that tuberculosis is one of the agents capable of producing the clinical and pathological changes characteristic of rheumatism. The observation of Bezançon and Weil (1930) and others of a clinical case of tuberculous rheumatism, in which an Aschoff nodule containing acid-fast bacilli was found at autopsy in one of the affected joints, appears to lend support to this view. No similar observation has since been reported, so far as I know. To A. Poncet (1903), however, and to the Medical School of Lyons, is generally given the credit for the introduction of tuberculous rheumatism in medicine. The French school certainly fought hard for its offspring and finished by attributing to it such far-reaching virtues as to induce much scepticism: "The first task when confronted by a case of rheumatism is to prove that it is not tuberculous" (Poncet and Leriche).

The "discovery" of a filterable phase of the tubercle bacillus (Fontes) lent impetus in Europe and in South America to the theory of a possible tuberculous aetiology of rheumatism. This discovery, however, remains unconfirmed (Topley, 1936). Then in the early 1930's came from Prof. Loewenstein's laboratory in Vienna a series of triumphant bulletins announcing the finding of Koch's bacillus in the blood stream in a variety of conditions, from disseminated sclerosis to rheumatism (Reitter and Loewenstein, 1933).

\* Grocco's original paper "Osservazioni su due forme cliniche dell'infezione tubercolosa," *Lo Sperimentale*, 1892, is not easily available in London. An important quotation from Grocco's paper, translated into French, can be found in Frugoni, C., and Peserico, E., "Rheumatisme et Tuberculose," *Acta rheumatol.*, 1932, 4, 9-14.

Naturally a flood of papers followed in Central and Western Europe, and in 1934 Pic from Lyons, published an article under the title of: "Rheumatisme et tuberculose; Évolutions des conceptions médicales de Bouillaud à Poncet, de Poncet à Loewenstein." In England, Copeman and Clay (1935) published two cases of rheumatoid arthritis believed to be of tuberculous origin, and followed this with a series of twelve cases in which the most important evidence of tuberculosis was the report of positive blood cultures from samples sent by him to Prof. Loewenstein's laboratories in Vienna (Copeman, 1936). He quoted at the same time the 1933 memorandum of the Medical Research Council (Wilson, 1933) which entirely disproved Loewenstein's findings, and pointed out that the positive blood cultures were only "important evidence of tuberculosis" if the reader chose to believe in the reliability of Loewenstein's method, but that there was also clinical evidence of tuberculosis in support. Copeman's conclusion was that a tuberculous factor should be considered in all cases of atrophic arthritis in which the aetiology is obscure. His paper includes an extensive bibliography and is a useful guide to English readers on the subject. In the United States, Brav and Hench (1934), reviewing the subject in 1934, came to the conclusion that "there was as yet no adequate clinical method of identifying tuberculous rheumatism, no consistent roentgenographic evidence, no experimental nor laboratory evidence in its favour that is not highly controversial, and no consistent demonstration of its supposedly characteristic microscopic pathology." This is, to my mind, an unduly pessimistic conclusion, as individual cases have been published in which the clinical evidence in favour of a tuberculous aetiology appears overwhelming (vide Copeman's review).

It is clear, therefore, that the condition is uncommon and that damage to the good reputation of tuberculous rheumatism has been done by the exaggerated claims which continental authors have made on its behalf, and by their attempts to bolster up their claims in more recent times with bacteriological findings which have been disputed and remain as yet unconfirmed (Wilson and Topley). The case I am presenting furnishes, I think, sufficient evidence for a diagnosis, on clinical grounds, of acute rheumatism (simulating Bouillaud's disease) of tuberculous origin. To the English-speaking readers it has an added interest in that the reports of W. S. C. Copeman and of Brav and Hench limit themselves to the consideration of a possible tuberculous aetiology in certain cases of rheumatoid (atrophic) arthritis, but do not describe, nor consider, cases of acute rheumatism of tuberculous origin.

## CASE HISTORY

A male aged 19 years, was admitted to the pleural effusion unit on March 3, 1943, from another hospital. Sudden onset of illness on Dec. 25, 1942, with pain in right hemithorax, malaise, and unproductive cough. Mid-January, 1943, developed pain in left hemithorax also with malaise, sweating, and a little fever. No joint pains. No sore throat. Treated at home by panel doctor up to Feb. 11, 1943, when he was admitted to hospital. There, diagnostic aspiration from left pleural cavity showed straw-coloured clear fluid with high protein content, and a predominantly lymphocytic cell count; the fluid was sterile (Loewenstein-Jensen culture also negative).

Past history was uneventful: chicken-pox, measles, and whooping-cough in infancy; not subject to recurrent colds or sore throats. He is an only son; parents are alive and well. No history of contact with known case of pulmonary tuberculosis. Had been a clerk up to March, 1942, when he became a sheet-metal worker. Hours of work from 8 a.m. to 6 p.m., with frequent overtime. This increase in his working hours often left him very tired.

On admission the patient was a well-built youth with an obviously toxic facies; moist, white, "transparent" hands; and recent loss of weight (on Feb. 3, 1943, weight 145 lb.; highest known weight 164 lb.; weight on Nov. 1, 1943, 170 lb.). There was a malar flush, slight cyanosis of finger-nails, but no clubbing of fingers. Occasional unproductive cough and some pain in the right hemithorax, of pleuritic type. T. 98.8° F.; P. 80-95, regular; B.P.  $\frac{110}{80}$ . The trachea was pushed to the right and there was diminished excursion of the left hemithorax. The apex beat was visible and palpable inside the nipple line. The heart sounds were pure, but the second pulmonary sound was loud and reduplicated. There were signs of a left pleural effusion of moderate size, and a loud, pleural-friction rub was heard at the right base. Apices clear. Abdomen well retractable; liver not palpable. No signs of free fluid in the peritoneum. Urine clear; no albumin or sugar. A skiagram of the chest showed normal heart shadow, small left pleural effusion, peaking of the right dome of diaphragm; no parenchymatous lesion observed. Tuberculin patch-test (Evans and Lescher) clearly positive after 48 hours. Erythrocyte sedimentation rate: 25 mm. first hour (Westergren).

Although there was no fever the disease was obviously still active nine weeks after its onset, and the patient was kept on absolute rest. On Feb. 6, 1943, his condition appeared to deteriorate; the temperature rose to 100° F. and the patient was listless and refused food. The physical signs in the chest were unchanged. On Feb. 9 pain and swelling appeared in the first interphalangeal joints of the first and second fingers of the left hand. The swellings were tender, not red, and there was some limitation of movement. Within the following twelve days these joints became involved in succession: right wrist and right hand, left ankle, left wrist, and right ankle; vague pains in elbows and knees but no visible swellings nor limitation of movement. As the other joints became involved, the first appeared to heal. During this time there was moderate fever (99°/100° F.); the pulse was regular at between 90-95 per minute, and the patient was clearly very ill. He started to improve by Feb. 22 when his temperature became normal and no swelling or tenderness could be found in the joints. A week later the improvement was marked. The patient has since made a slow but steady recovery. He is now

up and about half day and is allowed to perform some light engineering work in the ward. The left pleural effusion is clearing up, there remaining only some pleural thickening at the left base, while an adhesion holding up the middle part of the diaphragm is still seen in the skiagram of the chest. The heart is now central, of normal size and contour. No bruits have been heard at any time. Electrocardiogram is normal.

During the episode of acute polyarthritis treatment was confined to an occasional dose of neperthe to relieve pain, and to light splinting and warm wool around the affected joints. A throat swab gave less than 5 per cent. haemolytic streptococci. Antistreptolysin titre of serum 30 units. Blood count showed moderate secondary anaemia (Hb. 80 per cent.). White cell count was 7,600 per cmm. Differential white cell count was: polymorphs, 68 per cent.; basophils, nil; eosinophils, 1 per cent.; lymphocytes, 31 per cent.

## DISCUSSION

The diagnosis of this case, in the absence of any bacteriological proof of tuberculosis, rests on clinical grounds. The differential diagnosis is evidently between tuberculosis and rheumatic fever. The main point against a rheumatic aetiology is that it is difficult to imagine a bilateral rheumatic pleurisy persisting throughout many months, complicated by an episode of acute polyarthritis, not affecting the heart. Then, the onset of the illness was abrupt, with pleural pain not preceded by a sore throat or even vague joint pains. The episode of acute polyarthritis was short, especially as no salicylates were given. Since the end of February there has been no recurrence of general pain or swelling. Pain also appeared to be less severe in the affected joints for the degree of swelling than would have been expected in a comparable case of true rheumatic fever. A curious feature was that, while the proximal joints (shoulders and hips) were apparently not affected at all, and the elbows and knees were only subjectively involved, the wrists, hands, ankles, and feet, more distally placed, showed swelling and tenderness with limitation of movement. The low haemolytic streptococci in the throat, the white cell count, and the low antistreptolysin titre of the serum, all bear witness against a rheumatic aetiology. The diagnosis of tuberculous pleural effusion rests on the acute onset, on the chronicity of the condition, on the fact that both pleurae were involved, on the severity of the illness with a relatively low degree of fever, on the character of the pleural fluid, on the white cell count, and upon a positive skin reaction to tuberculin. It is, of course, the whole picture and not any single feature which is diagnostic. Is there any reason, apart from obstinate prejudice, for postulating a different aetiology for the polyarthritis? I can find no such reason.

While the diagnosis of acute tuberculous rheumatism appears to be fairly certain, I feel that it would be idle, in the absence of bacteriological and pathological proof, to make any pronouncement on the pathogenesis of this case, whether it be a tuberculous bacillaemia or an allergic reaction to tuberculous toxin. Clinical proof of bacillaemia would

have been the development of true tuberculous arthritis in one of the affected joints, but this did not happen.

The experience at Sidcup of over 350 consecutive cases of tuberculous pleural effusion (Heaf and Ellingworth, 1944) shows that transitory tuberculous bacillaemia is not uncommon in the course of this disease. Apart from the more obvious cases of discrete or frank miliary dissemination, distant bone and joint lesions and tuberculous bacilluria, the incidence of lung foci of presumed haematogenous origin is relatively common. I have also twice observed transitory monarticular swellings—one of a knee, the other of an ankle—with complete resolution within three weeks, and I confess to a great reluctance in ascribing these swellings to allergy. A sudden allergic flare-up due to exogenous reinfection—if such an event ever really occurs—can be excluded with some degree of confidence, as it is a strictly observed policy at Sidcup not to admit or retain open cases of pulmonary tuberculosis. Finally, the low eosinophil count is not in favour of an allergic reaction. On the other hand, we all know that allergic phenomena do occur during the course of tuberculous disease. While confessing to a personal bias towards the bacteriaemic pathogenesis, the experimental aspects of rheumatism, allergic phenomena and their related problems are so complicated and full of pitfalls that I feel that further discussion of these points would be unfruitful. It is therefore best to limit this discussion to the observed clinical facts, and the facts, I think, lead to a diagnosis of "tuberculous rheumatism" in this case.

#### SUMMARY

A brief historical outline of the vicissitudes of tuberculous rheumatism is given, with the reasons

for naming this condition Grocco-Poncet rheumatism. It is recalled that a tuberculous aetiology has been described not only in cases of rheumatoid (atrophic) arthritis but also in cases of acute polyarthritis simulating rheumatic fever. The conclusion is reached that tuberculous rheumatism is a true clinical condition, but that the claims made on its behalf by the Lyons' Medical School and by other continental authors are grossly exaggerated.

A personally observed case of tuberculous pleural effusion is described, in the course of which an acute polyarthritis occurred, simulating rheumatic fever, with complete resolution. The diagnosis of tuberculous rheumatism in this case is discussed and upheld. No conclusions as to the pathogenesis of this case, whether through bacteraemia or allergy, are arrived at, but the writer's personal bias towards a hypothesis of tuberculous bacteraemia is confessed.

The L.C.C. is in no way responsible for the views expressed in this paper.

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#### BOOK REVIEW

*The Arthropathies; a Handbook of Roentgen Diagnosis.* By Alfred A. de Lorimier, A.B., M.A., M.D. Colonel Medical Corps, American Army; Commandant, the Army School of Roentgenology, Memphis, Tenn.; Formerly Director, Department of Roentgenology, Army Medical School, Washington, D.C. \$5.50. The Year Book Publishers, Inc., Chicago.

This work is one of a series of six covering the whole field of diagnosis by the use of x-rays written by acknowledged experts in each branch. It is dedicated to all doctors possessed of scientific enthusiasm having primary interest in the patient; secondary, but closely equivalent, interest in the underlying pathology; and least interest in their personal gain in handling the case.

The foreword stresses the importance of the radiographer having the assistance of the clinical and laboratory data in attempting to arrive at a diagnosis, a matter of great importance too often thought to be quite unnecessary. Abnormalities as well as diseases are dealt with, and illustrations are on a lavish scale, for the most part reproductions of x-ray photographs but also some useful anatomical diagrams. In the study of the film the appearance of the soft tissues is first described, followed by those of the bones and joints; the appearances are differentiated into those that are likely to be seen and those that may possibly occur, and the difference between the early and late stages are clearly described. This is

followed by the incidence, history, physical and laboratory findings, and clinical course, thus supplying a clear picture of the morbid condition under study, concise but astonishingly complete. The development of bones and joints in the embryo is described and the bearing this may have in pathological changes in later life. Every known disease or disorder of joint structures seems to have been included in the author's survey, with a bibliography to each, so that fuller descriptions may be consulted where necessary.

Many radiographers will appreciate the general discussion of technique, the effects of difference in kilovoltage and other factors; and the directions for routine analysis of the appearances in the film are a valuable guide to the practitioner in arriving at a diagnosis. The reproductions of typical radiographs are on the whole good and clear in detail. The system of placing the letter identifying the particular feature in the picture after the description of that feature is contrary to the usual practice and apt to be confusing at first, but this is a minor detail.

A book of this kind is essential to any doctor interested in the diseases of joints, and this volume can be cordially recommended for its compactness, clearness of description, wide scope, and its reasonable price.

C. W. B.

